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DATE: Tuesday, June 21, 2005

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<input type="checkbox"/>	L2	L1 and pneumoni\$	153
<input type="checkbox"/>	L3	L2 and (\$triad or coil\$)	15

END OF SEARCH HISTORY

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❑ 3. [20040005331](#). 13 Mar 03. 08 Jan 04. Vaccine compositions comprising Streptococcus pneumoniae polypeptides having selected structural motifs. Johnson, Leslie S., et al. 424/190.1; 530/350 536/23.7 A61K039/02 C07H021/04 C07K014/315.

❑ 4. [20040001836](#). 14 Apr 03. 01 Jan 04. Vaccine compositions comprising streptococcus pneumoniae polypeptides having selected structural motifs. Johnson, Leslie S., et al. 424/165.1; 424/190.1 A61K039/40 A61K039/02.

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US006833356B1

(12) **United States Patent**
Koenig et al.

(10) Patent No.: **US 6,833,356 B1**
(45) Date of Patent: **Dec. 21, 2004**

(54) **PNEUMOCOCCAL PROTEIN HOMOLOGS
AND FRAGMENTS FOR VACCINES**

(75) Inventors: **Scott Koenig**, Rockville, MD (US); **Jon Heinrichs**, North Potomac, MD (US); **Leslie S. Johnson**, Germantown, MD (US); **John E. Adamou**, Germantown, MD (US)

(73) Assignee: **Medimmune, Inc.**, Gaithersburg, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 197 days.

(21) Appl. No.: **09/645,835**

(22) Filed: **Aug. 25, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/150,750, filed on Aug. 25, 1999.

(51) Int. Cl.⁷ **C07K 14/00; A61K 38/16**

(52) U.S. Cl. **514/12; 514/2; 530/350; 424/184.1; 424/130.1; 424/243.1; 424/244.1; 536/23.1**

(58) Field of Search **514/12, 2; 530/350, 530/23.1; 424/184.1, 130.1, 243.1, 244.1, 185.1; 536/23.1**

(56) **References Cited**

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2003/0031682 A1 * 2/2003 Brodeur et al. 424/190.1

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Spellerberg et al., Lmb, a protein with similarities to the Lral adhesin family, mediates attachment of streptococcus agalactiae to human laminin. Infection and Immunity Feb. 1999, vol. 67 871-878.*

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Primary Examiner—Robert A. Wax

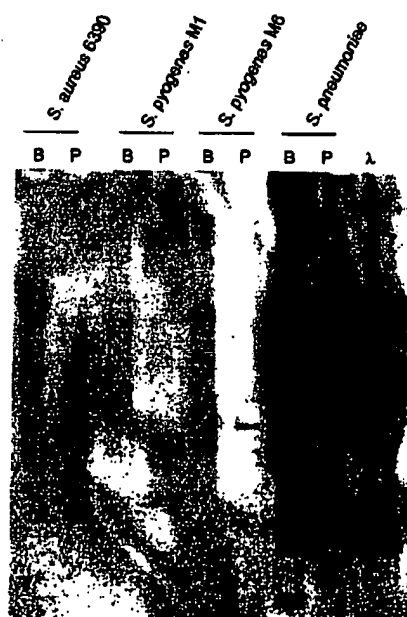
Assistant Examiner—Chih-Min Kam

(74) Attorney, Agent, or Firm—Elliott M. Olstein; Alan J. Grant

(57) **ABSTRACT**

The invention is directed to isolated polypeptides bearing sequence homology to the Sp36 protein found in pneumococcal organisms, such as *Streptococcus pneumoniae*. Polynucleotides encoding such polypeptides are also disclosed. The invention also relates to antibodies specific for the disclosed polypeptides and to uses of such antibodies in the treatment of diseases caused by staphylococci as well as group A and B streptococci. In addition, the invention relates to the use of the disclosed polypeptides in compositions and as vaccines and for prophylactic uses such as in vaccination of animals, especially humans, against a wide variety of streptococcal, staphylococcal and other diseases.

8 Claims, 9 Drawing Sheets



-continued

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Leu	Leu	Lys	Gly	Ser	Asn	Pro	Ser	Ser	Val	Ser	Lys	Glu	Lys	Ile	Asn
				805					810					815	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 4 and wherein said polypeptide binds to an antibody that is specific for Sp36 (SEQ ID NO: 7).

2. An isolated polypeptide comprising an amino acid sequence with at least 95% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 2 and 4 wherein said polypeptide is identical to that found in an organism selected from the group consisting of Group A streptococci and *Staphylococcus aureus* and wherein said polypeptide binds to an antibody that is specific for Sp36 (SEQ ID NO: 7).

3. The isolated polypeptide of claim 2 wherein said Group A organism is *Streptococcus pyogenes*.

4. The isolated polypeptide of claim 2 wherein said organism is *Staphylococcus aureus*.

25 5. An isolated polypeptide comprising an amino acid sequence at least 95% identical to the sequence of SEQ ID NO: 4 and wherein said polypeptide has a sequence with at least 12.6% sequence identity to the amino acid sequence of the Sp36 protein (SEQ ID NO: 7) of *Streptococcus pneumoniae* and wherein said isolated polypeptide binds to an antibody that is specific for Sp36.

30 6. An isolated polypeptide comprising the sequence of SEQ ID NO: 2 wherein said isolated polypeptide binds to an antibody that is specific for Sp36 (SEQ ID NO: 7) of *Streptococcus pneumoniae*.

35 7. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

40 8. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4.

* * * * *



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DATABASE BROWSING

EBI Dbfetch

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OC  Bacteria; Firmicutes; Lactobacillales; Streptococcaceae; Streptococcus.
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RA  Choi G.H., Barash S.C., Rosen C.A., Masure H.R., Tuomanen E., Gayle A.,
RA  Brewah Y.A., Walsh W., Barren P., Lathigra R., Hanson M., Langermann S.,
RA  Johnson S., Koenig S.;
RT  "Use of a whole genome approach to identify vaccine molecules affording
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RL  Infect. Immun. 69(3):1593-1598 (2001).
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[0077] The identification of multiple coil structures of alpha helical amino acid segments in the S. pneumoniae polypeptides according to the invention may be determined by the location of proline rich areas with respect to one another. Further the "X" area optionally located between two or more alpha-helical structures can play a part in the formation of a coil within a coil structure. Standard three-dimensional protein modeling may be utilized for determining the relative shape of such structures. An example of a computer program, the Paircoil Scoring Form Program ("PairCoil program"), useful for such three-dimensional protein modelling is described by Berger et al. in the Proc. Natl. Acad. of Sci. (USA), 92:8259-8263 (August 1995). The PairCoil program is described as a computer program that utilizes a mathematical algorithm to predict locations of coiled-coil regions in amino acid sequences. A further example of such a computer program is described by Wolf et al., Protein Science 6:1179-1189 (June 1997) which is called the Multicoil Scoring Form Program ("Multicoil program"). The MultiCoil program is based on the PairCoil algorithm and is useful for locating dimeric and trimeric coiled coils.

*Reconsider*

Search Results - Record(s) 1 through 5 of 5 returned.

-
- ☐ 1. 6773880. 03 Jan 01; 10 Aug 04. Streptococcus pneumoniae 37-kDa surface adhesion A protein. Sampson; Jacquelyn, et al. 435/6; 536/23.7 536/24.32 536/24.33. C12Q001/68.
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- ☐ 2. 6582706. 21 Dec 99; 24 Jun 03. Vaccine compositions comprising Streptococcus pneumoniae polypeptides having selected structural MOTIFS. Johnson; Leslie S., et al. 424/244.1; 424/184.1 424/185.1 424/190.1 424/237.1 435/320.1 435/69.1 530/350 536/23.1 536/23.7. A61K039/09.
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- ☐ 3. 6406883. 25 Sep 98; 18 Jun 02. Lmb gene of Streptococcus agalactiae. Luticken; Rudolf, et al. 435/69.1; 424/244.1 435/243 435/252.3 435/253.4 435/320.1 435/69.3 536/23.7. C12P021/06.
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- ☐ 4. 6217884. 28 Dec 98; 17 Apr 01. Streptococcus pneumoniae 37-kDa surface adhesin a protein. Sampson; Jacquelyn S., et al. 424/244.1; 424/184.1 424/190.1 424/200.1 435/69.1 435/69.3 435/71.1 530/350 536/23.7. A61K039/09.
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- ☐ 5. 5854416. 17 Sep 96; 29 Dec 98. Streptococcus pneumoniae 37-KDA surface adhesin a protein and nucleic acids coding therefor. Sampson; Jacquelyn S., et al. 536/23.7; 424/244.1 435/320.1 536/23.1. C07H021/04.
-



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Identities = 211/357 (59%), Positives = 271/357 (75%), Gaps = 11/357 (3%)

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Q8IJ56			
Q6FNC8			
Q6CTI8			

National App. No.

PCT/CA 99/01218

CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/31 C12N15/62 C07K14/315 A61K39/09

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CAB Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 18930 A (HUMAN GENOME SCIENCES INC ;CHOI GIL H (US); HROMOCKYJ ALEX (US); J) 7 May 1998 (1998-05-07) cited in the application SP103; SEQ ID NOs. 181 and 182; page 85, line 14 - line 42; claims 1-21; table I SEQ ID Nos. 65 and 66;	1-12
X	WO 98 18931 A (DOUGHERTY BRIAN A ;HUMAN GENOME SCIENCES INC (US); ROSEN CRAIG A () 7 May 1998 (1998-05-07) SEQ ID No. 192 claims 1-20 SEQ ID No. 94	1-12

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" documents which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

28 June 2000

Date of mailing of the international search report

24.07.00

Name and mailing address of the ISA

European Patent Office, P.B. 5518 Patentlaan 2
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Fax: (+31-70) 340-3018

Authorized officer

Hornig, H

Table 1

62

AGAAGCCTATTGGAATGGGAAGCAGGGATCTCGTCTTCTTCAAGTTCTAGTTATAATGCAAAATCCAGC
TCAACCAAGATTGTGAGAGAACCACAATCTGACTGTCACTCCAATTATCATCAAAATCAAGGGGAAAA
CATTTCAAGCCTTTTACGTGAATTGTATGCTAAACCCCTTATCAGAACGCCATGTGGAATCTGATGGCCT
TATTTTCGACCCAGCGCAAATCACAAGTCGAACCGCCAGAGGTGTAGCTGTCCCTCATGGTAACCATT
CCACTTTATCCCTTATGAACAAATGTCTGAATTGGAAAAACGAATTGCTCGTATTATCCCTTCGT
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TCCAAGTCCGCAACCTGCACCAAATCCTCAACCAGTCCAAGCAATCCAATTGATGAGAAATTTGGTCAA
AGAAGCTGTTTGAAGTAGGCGATGGTTATGTCTTTGAGGAGAATGGAGTTTCTCGTTATATCCCAGC
CAAGGATCTTTTACGAGAAACAGCAGCAGGCATTGATAGCAAACTGGCCAAGCAGGAAAGTTTATCTCA
TAAGCTAGGAGCTAAGAAAACGACCTCCCATCTAGTGATCGAGAATTTTACAATAAGGCTTATGACTT
ACTAGCAAGAATTCACCAAGATTTACTTGATAATAAAGGTCGACAAGTTGATTTTGAGGCTTTGGATAA
CCTGTTGGAACGACTCAAGGATGTCNCAAGTGATAAAGTCAAGTTAGTGGANGATATTCTTGCCTTCTT
AGCTCCGATTTCGTATCCAGAACGTTTAGGAAAACCAAATGCGCAAAATACCTACACTGATGATGAGAT
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CATACCTCATTATGACCATTAACATAACATCAAATTTGAGTGGTTTACGAAGGCCTTTATGAGGCACC
TAAGGGGTATATCTCTGAGGATCTTTTGGCGACTGTCTCAAGTACTATGTGCAACATCCAAACGAAACGTC
GCATTGAGATAATGGTTTGGTAAACGCTAGCGACCATGTTCAAAGAAAACAAAAATGGTCAAGCTGATAC
CAATCAAACGGAACCAAGCGAGGAGAAACCTCAGACAGAAAACCTGAGGAAGAAACCCCTCGAGA
AGAGAAACCGCAAGCGAGAGAAACAGAGTCTTCAAACCAACAGAGGAACAGAAAGATCACCAGAGGA
ATCAGAAGAACCTCAGGTCGAGACTGAAAAGGTTGAAGAAAACCTGAGAGAGGCTGAAGATTTACTTGG
AAAAATCCAGGAT

SP042 amino acid (SEQ ID NO:66)

CSYELGRHQAGQVKESNRVSYIDGDQAGQKAENLTPEVSKREGINAEQXVIKITDQGYVTSBGDHYH
YNGKVPYDAIISEELMKDPNYQLKDSDIVNEIKGGYVIKVNKYVYLKDAHADNIRTKKEIKRQK
QERSHNHNSRADNAVAARAQGRYTTDDGYIFNASDIIEDTGDAYIVPHGDHYHIYPKNLSASELAAA
EAYWNGKQSRPSSSSSYNANPAQPRLESENHNLTVPTPHQNGENISSLLRELYAKPLSERHVESDGL
IFDPAQITSRTARGVAVPHGNHYHFIPEQMSLEKRIARIIPLYRSNHWPDSRPEQPSQSTPEPS
PSPQPAPNPQPAPSNPIDEKLVKEAVRKVGQGVFEENGVSRYIPAKDLAETAAGIDSKLAKQESLSH
KLGAKKTDLPSSDREFYNKAYDLLARIHQDLLDNKGRQVDFEALDNLLERLKDVKSDKVLVXDILAF
APIRHPERLKGKPNQITTYTDEIQVAKLAGKYTTEDGYIFDPRDITSEGDYVTPHMTSHWIKKDSL
SEAERAAQAYAKEKGLTPSTDHQSNGTEAKGAEAIYNRVKAAKKVPLDRMPYNLQYTVVKNGLSLI
IPHYDHYHNKIFEFWDEGLYEAPKGYTTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKGQADT
NQTEKPSSEKPKTEKPEEETPREKPKSEKPEPKPTEPEEPESEEPQVETEKVEEKLREAEDLLG
KIQD

SP043 nucleotide (SEQ ID NO:67)

TTATAAGGGTGAATTAGAAAAAGGATACCAATTTGATGGTTGGGAAATTTCTGGTTTCAAGGTAAAAA
AGACGCTGGCTATGTTATTAATCTATCAAAAGATACCTTTATAAAACCTGTATTCAAGAAAAATAGAGGA
GAAAAAGGAGGAGAAAAATAAACCTACTTTTGATGTATCGAAAAAGAAAGATAACCCACAAGTAAACCA
TAGTCAATTAATGAAAGTCACAGAAAAGAGGATTTACAAAGAGAAGAGCATTCACAAAAATCTGATTC
AACTAAGGATGTACAGCTACAGTCTTGATAAAAAACAATATCAGTAGTAAATCAACTACTAACAATCC
TAATAAG

SP043 amino acid (SEQ ID NO:68)

YKGELEKGYQFDGWEISGFEGKKDAGYVNLKDTFIKPVFKKIEEKKEENKPTFDVSKKKDNPQVNH
SQLNESHKEDLQREEHSQKSDSTKDVATVLDKNNISSKSTTNPNK

SP044 nucleotide (SEQ ID NO:69)

GAATGTTTCAGGCTCAAGAAAGTTCAAGGAAATAAAATCCACTTTATCAATGTTCAAGAAAGGTGGCAGTGA
TGCGATTATCTTGAAGCAATGGACATTTTGCCATGGTGGATACAGGAGAAGATTATGATTTCCACAGA
TGGAAAGTGATTCTCGCTATCCATGGAGAGAAGGAATTGAAACGCTTTATAAGCATGTTCTAACAGACCG
TGCTTTTCGTCGTTTGAAGGAATTTGGGTGTCCAAAACTTGATTTTATTTTGGTGACCCATACCCACAG
TGATCATATTGGAAATGTTGATGAATTACTGTCTACCTATCCAGTTGACCGAGTCTATCTTAAGAAATA

1157

TGTCAGAATT AACATCTCCA AACGCTGTTT TTGAATCGGT CATTCTGATA CCATTTTCTG 10200
CACAATAAAC CAATACACGA TTATAGGCTT CTGTAGATTT AACCACTATA TACAATTCAA 10260
TCATTTTAGA ACGATTTTGC AGATATTTT TTAGTGTTG GAACATGGAT ATCACACCCC 10320
AAACAGAAAT GGCTACTAAA AGAGCTCCCT CATAAGG 10357

(2) INFORMATION FOR SEQ ID NO: 192:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6867 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

CGGGACATTC TCAATCTTCT CTCTTTTGT TTTCTCTTCT TTCTATGATA CAATGGAAAA 60
AATAAATTCA AAAGGAGTTT TTTTATGACT TATCCAAATC TCTTGGACCG CTCTTAACC 120
TATGTTAAGG TCAACACGCG CTCTGATGAA CACTCTACTA CTACTCCAAG TACACAGAGT 180
CAGGTTGACT TCGCAACAAA TGCCTAATT CCTGAAATGA AACGTGTTGG ACTGCAAAAT 240
GTTTACTATC TACCGAATGG TTTTGCTATT GGAACCTTGC CAGCCAACGA TCCGTCTTTA 300
ACACGTAAGA TTGGTTTAT ATCGCACATG GATACTGCTG ATTTTAATGC TGAAGGAGTC 360
AATCCACAGG TAATTGAAAA CTACGATGGT GGTGTGATTG AACTAGGGAA TTTGTGTTTC 420
AAACTCGATC CAGCTGACTT CAAGAGTCTT GAAAAATATC CAGGACAAAC GTCATCACA 480
ACAGATGGAA CAACCTTGCT AGGTGCTGAT GACAAGTCAG GAATTGCTGA AATTATGACA 540
GCCATTGAAT ATCTAACTGC TCATCCTGAA ATTAAGCACT GTGAGATTGG TGTGTTTTT 600
GGTCCAGATG AAGAAATCGG TGTGTTGCC AATAAATTTG ATGCAGAAGA TTTGATGTG 660
GATTTTGCTT AACTGTGTA TGGTGGTCCA CTAGGTGAAC TTCAGTACGA GACTTTCTCA 720
GCCGCTGGTG CTGAATTGCA TTTCCAAGGT CGTAATGTCC ACCCTGGTAC TGCCAAAGGG 780
CAGATGGTCA ATGCCCTTCA GCTAGCAATT GATTTTCATA ATCAACTTCC AGAAAATGAC 840
CGACCTGAGT TAACTGAAGG TTACCAAGGT TTTTACCATC TAATGGATGT GACAGGTAGT 900
GTTGAGGAGG CGCGTGCAAG CTACATCATT COTGATTTTG AAAAAGATGC CTTTGAAGCG 960
CGTAAAGCAT CCATGCAATC TATCGCTGAT AAGATGAATG AAGAACTGG GAGCGACCGT 1020
GTCACTCTCA ACTTGACAGA CCAGTACTAC AATATGAAAG AAGTCATTGA AAAAGATATG 1080
ACTCCAATTA CCATGCTTAA AGCCGTTATG GAAGATCTAG GTATCACGCC TATTATCGAA 1140

1158

CCAATCCGGG GTGGAACAGA CGGCTCTAAG ATTTCCCTTTA TGGGAATCCC AACTCCGAAT	1200
ATCTTTGCAG GTGGCGAAAA TATGCACGGA CGTTTTGAAT ACGTTAGCCT TCAGACTATG	1260
GAACGTGCAG TTGATACCAT CATTGGCAGT GTAGCTTATA AAGGCTAAAA AGACGAGGTA	1320
GCTCAGCTAC TTCGCCTTTC TTTTATTCT ACTGCTTTT CTTGATTTCC AGTAGTTGTA	1380
GAAGATTCTG TTGTTTCATT TTCTGAAGT GATTCAGCAG GPTTAGAATC TCTGTATTG	1440
CTTGGTTTGT TTTGTCGCT AGCAGTTCA ATGTTAGATT CTGCAGTTGC GTTTCGTTGG	1500
TTCTCAGCAC TGGTGTATC ACCATTGCT TCAGCATTC TTGCTGGACT TGTTCCTCA	1560
CTTGGCTAG CTTTGTAGTG GATTTGATGA TTCAAACTA GAATAGCTTT TGTGATTTCA	1620
AGTAAAGCTG TTTTGTCTT ACTCTTAGCA GAAAGTTGAT CTAATAATGC ATCCACCTTA	1680
TCAAAGTCCG CATCAGATCC ATTATTACTT TCTAAATAAG AGTGAAGCGA CATGAGAATA	1740
TCGTAGAGT TTTGATAGAG TACAAOTGTC TGAGGATCTT GCTCAGCATT TTCCTTTCT	1800
TGTTGAAGGG CGCTAGCGAT ACGAGTCAAG ACATCTTTTA CCTGACTGTT TACTTCATCC	1860
AAGTCTGCAT CAGCCTTGT TGTGGCAGCT TTTAGATTT CTACTTCTTC TGCCAAGGAT	1920
TGCTGATTC CTTCTTCATG GATTTGTTCC AAGAGTTGAT TTGCCTTGCT CAAAAGACTT	1980
TCTACTCTT CCTTGCTATC TGTGCGAGAT TATTGGTTGC TATCTACCAT GTACTCCTAA	2040
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TCTTTGTAGA TGCTCTGCT ATCAGCTAGA AGTTGATCTA CTTTGGCCAA GACTGCCTTC	2340
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ACATATGTGG CTGCTAATTC ACCTGCCGAC AAGTCACTCT CAGGAATGAA ATGATAGTGA	2760
CCACCATGTG GTACTATAGT AGATTGAAAT AGAATATGAG CAAATTGATA AGGGGATTTT	2820
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TATATAACCA TCATCGGTAG TATAACGTCC CTGTAATTTT GCTACAGATA CTCTGCACT	2940

1159

AGCTCCTTTA TCGTCTTTAC CATGTTCTTG TTTTGGCGA TTGATTTCAT CTTTGTTCG	3000
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AATATATCCT CCCTTAACCT AACTGACGAT ATCTTGATCT TCGGCTGAT AGTTGGGGC	3120
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ATAATGATCG CCATGAGAAG TTACATAACC TTGATCTGTA ATCTTAATAA CAATTTGTTT	3240
TGCTTGAATT CCTTCTTTTT GACTAACCTA GTCTGGAGTC AAATTTTCAG TCTTCTTAGT	3300
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TTCTGTGGT TGGTTCTCAA CTGTCCAGT AGTACTTTT CCATTTTCAG ATGGTTTATT	4020
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TCCCGATGGT AAATATAATT CAATGTTCC GTCCATATTA AACAGACAT TTTCTAGCTT	4140
CATCCCATAA CTTTCAGCAA ATTTTGCTAC TTTTCTTGT ACAGGATCCA CTGTAGGAAC	4200
TTCTTCTAAC GTTGAATTAC TAGTACTATT CCCAGTTCA GAAAGTTTT CTTTTCTAC	4260
CTTCTACTA GTCTTTGGTT CTTCTACCTT TTCATCAAGT TTTAAGTTTT CTGTGCTTT	4320
ATTCCTTTTA AATGTGGTA GAATACTGG TTTATCAGT TCATTTTCTT TTTCCAAGAT	4380
AGGTACTTCC ACAATATAAG TCGATTGATT GTCCAAATAA GCATTTGCCA TGAAGTTAC	4440
AGGAATTTTA TTTCCGCCG TTCTGGTGT TCCTTGGTT AATTTCCGAA TCGGTAATTT	4500
GATTTCAACA ACTTTATAGT TATTTTCTAA ATAAGCATTT CCATGAAAT CATCAAACAC	4560
TCTGACTAAA GCATCAGTTC CTTTAGGCAC TGCAAATTGA GGCTTCACTC TTAATAAGT	4620
ATCCCTGCA TGGAAAGGAT AGAAAATCGT TTGACTGGCC ATTTTGTAAAG CTAAAGAGGT	4680

1160
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TCCTTCTCCA AATACTTTAC CAGATACTTT CTCCAATACT TTCCATCTG GTGTATTAA 4860
TTTACTAGC ATATTGATAC CTAATTTTTT CTCCAATICA GCGGAAAAC TAAAAGAAAC 4920
GCGTTTTTGA CCATTGGCTA GAGTAAAGTT TTGATTATTA AACGTACTAT TTTTAAACAA 4980
ATTAACAACA TTCGTAAAT CTCTCCAGT ATAAACTTTA TTCCCTTCTT TTTTAGCAAC 5040
TCCTTCTTCG GGTTTAAACA GTTCATAGTT ACTGTGAGAA TGACCAATTC CAACCGGTTT 5100
ATGTCATCA ATCGGATCTG CATGATGGTG ATCTCCATGC GGATAAATAA TCGCATTTTT 5160
TTCTTTATTC ACGACAATAC TTTCACGTTT GACCCATAT TGTTCATAA TGCCAGCAAT 5220
TTTTTCTTCG ATTTTTTTAT CTAATCTTTT CATTTCTTTG GCATTACTTG GATAATCCTG 5280
TTCATGAGAT GACAAGAAT CTAATCCATT ATGACTAGTT TTAACCTCCT CTAATGTTT 5340
TTGCGCASC TAAATTGCTC TTCTGTCAAG TCCTTCTTGA AGAAATAATG ATTGTGCTCT 5400
CCGTGACTCA TGACAAAACC TGATTCATCT TCAGCGATAA TACGATTAGC ATCAAATCCG 5460
TATCCATCTT CTTCATGTTT CTCATGTGAA GTTCTTGGAT TGATTGGAAG AGATGGAGAA 5520
GGTGTGCTA GACTATTGTT TGGAAGAGTC GGTGCCCCAA TTTGATTGA TTTTGAATG 5580
TAATGGAAAT GATCACCATG TCTTACAATA TAAGCTGTAG CCGTTTCTTC AACGATATCT 5640
TTTGGATTAA AAATATAACC ATCAGATGCT GAAGAGAGCT CCTTACTTGT CGTTAAAGAA 5700
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GAAACTGTAG AACCACTCC ACTGATAGGC ACCATTCTGG CAATCTTTTC TTCTAAGGCA 5820
GAAAGCTTGC TGTAAAGAAAT AAAGTGGTAA TGGTCGCCAT GCGGAATCGC AACTCCATTT 5880
GGTGTACGAC TGATAATCTT AGCAGGGTCA AAGACCAGGC CATCTGATTC ACTGTAACGT 5940
TGGCCGCTAG GTGAATCATA GAGTTCCCTC AAAAGACTCT GGAGATTTTC AGATTTATTT 6000
GCTGCGCTGC TAGTTCATCC TTTTGCTACA GATTGCGTGT TATTGTCACT AGCTGTTGAA 6060
GAATAGCTTA ACTGACTCGG TTGCATATTT TTCCAGCCA GATGTGCTTT AGCTGCTGCT 6120
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GTCGTATATC GTCCCTGAGA CCTTGCTACA GCAACATTAG AGTTAACCTT CTCATTATCT 6300
TTGACATGTT CTGTTTTTG ACCATTGATT TCATCTTTAG TTCGAACATT ATCAGCATGA 6360
GCTGCATCTT TCAGGTAGAC ATAATATTTT CCATCGACCT TGATGATATA ACCACCCCTG 6420
ACTTCATTGA CAATATCAGC GTCTTTAAGT TGATAGTTTG GATCCTTCAT CAAGAGTTCT 6480

1161

TCACTAAAGA GGGCATCATA AGGAACTTTC CCATTATAOT AATGATAGTG GTCACCGTGT	6540
GACGTTACAT AGCCCTGATC TGTAAATTTG ATTACAAATT GCTCAGCCTG AATTCCCTCT	6600
TTCTGGCTAA CCTGGTCTGG TGTCAAGTTT TCACTTTCTT GACTTGACTG GCTGCCATCC	6660
ACATAAGAGA CACGATTATT GTCCTTATTT TCCTGCCAAC GATGCTGCTT TAGTGCATAG	6720
GCACATAGAC TCAAGGATAC GATAACAGCT GATCCAGCTG CTATATATTT TTTACTAAAT	6780
TTCATAAATC CCTCATTTCA ATAAATGATG AAGTTTTCCT TCAACTTCTT TTACTTTATT	6840
AAATAGTTT CTAAACCCGG GGGTACC	6867

(2) INFORMATION FOR SEQ ID NO: 193:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 999 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

CGTTCTAAAA ATGCAGTACG TTTGATTGAG AAATCAGTTA AAGGTATGCT TCCACACAAT	60
ACACTTGGAC GCGCTCAAGG TATGAAGTTG AAAGTATTTG TTGGAGCTGA GCACACTCAC	120
GCTGCACAAC AACCAGAAAT TCTTGACATT TCAGGACTTA TCTAAGGAAA GGAACAATAA	180
AGTATGTCAC AAGCACAATA TGCAGGTACT GGACGTCGTA AAAACGCTGT TGCACGCGTT	240
CGCCTTGTTC CAGGAACTCG TAAATCACT GTTAACAAAA AAGATGTTGA AGAGTACATC	300
CCACACGCTG ACCTTCGTCT TGTCAACAAC CAACCATTCG CAGTTACTTC AACTGTAGGT	360
TCATACGACG TTTCGTTAA CGTTATAGGT GGTGGATACG CTGOTCAATC AGGAGCTATC	420
CGTCACGGTA TCGCTCGTGC CCTTCTTCAA GTAGACCCAG ACTTCCGCGA TTCATTGAAA	480
CGCGCAGGAC TTCTTACACG TGACTCACGT AAAGTTGAAC GTAAGAAACC AGGTCTTAAG	540
AAAGCTCGTA AAGCATCACA ATTTAGTAAA CGTTAATTCG AAAGAATTAC TATACTTATA	600
CAGAGCACCT TTCGGGGTGT TCTTTTCTTA TACTTTCTTA CTAAATGGT GCAATTGACA	660
CAGTTGTTGC GACTTTAGTC GCTTACAAAT GTGGCTGCAA CCTGACATGG TCAGTTGCCT	720
CAAAACGTTA ATCAATACGA TTATATCAAC GTTCAAAGC ACTCAAGGGT TTACCCTATG	780
GGTGCTTTTT TCTATACTTT CTAAAAAAGT TTACCCTAAA ATTTGCCCTA AAATTACCCT	840
ACTTATTTTT AAGATGTTGG TAGGCAACTT GTCCAGCAGA TAATGGAACT ATGTTTGAAG	900
TATTAACATA AGTCTTAGTT GTAACGGTAT CGCTATGAGT TAATGCTTCA GAAATGGCTT	960

727

GCTGCTGGAC TAGCTGCTTC ACCATTGTTT TTAGGATAGT CAGAAATATA GCTTAATTTT 9780
CCAGTCCATT TTTTATCAGG ATACACTTTA GAAGTAAAGC TTACTTCTTG ACCTACAGAA 9840
AGGTTGGCTA GATTGTACTC AGACAATTCT CCCTTGACTT GTAAATTTTC ATTGCTGACA 9900
ATATGAACCA TAACTTGACT CGCCCCGTGT GGAGATTAG AAACATTGCT ATTGACTTCG 9960
AOCACAGTTC CCTCTAGGGT ACTGAGAACA GTTGTTCAT CCAATTGACT TTGAGCCTTG 10020
CTTAATTGGG CCGCAGCATC TGCACGCGCA TCACGGGCAT CACCCAATTG AGCGTCAATA 10080
GAAGCAACAG AATTTCAGC CACTGGAGTT GGGCTTTCCA CCGTTGCATC TTCTCTCTCT 10140
ACTGGCGCTG GTAACGTGG AGCCGGAGCT GAAGCGGCTT CATTCGTGC TTGATTGACT 10200
TCATTGATAT GACGATCTGC CCTAGTACT GCTCGACTAG CTGAATCATA GGCCGCTGTC 10260
GCTTCTGAAC TACTGTACTT GACTAAAGCC TGCCCTTCGC TGACCTTATC GCCCACAGAA 10320
ACAAGGATTT CATCTAAATC ACCCTTACTA GCATCAAAT AAACATATTG TTCATTTTTT 10380
GCTGTACTG TCCCTGACAA TAAACAGAG GAGGCCACGC TTCCTTCCTT GGCAACAACA 10440
AGATGAGTAG GCTCATCTTT TAGAGCAGTC TGAGAAGGTT GTCTAAAGAG TAAATCCCC 10500
CCAGCACCCA ATACAATAC ACTCGCAGCA CCGATTGCTG CATAAGITG CCACITTTTA 10560
GCTTTACCAT TCTTTTCTT CATAATGAAA CTCCTTTTCT TTTTACAAT ACTTTGCTAT 10620
TATACCAAT TTCCTCCAG CAAACAATAC AGTTCAGGAT TAAACAATCG TTCGGAATTT 10680
TGCTTTTCGG 10690

(2) INFORMATION FOR SEQ ID NO: 94:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8195 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

GAGAAAGCGC CCACGTTCC CCGAAGGGAG AAAGGCGGAC AGGTATCCGG TAAGCGGCCA 60
GGGTCCGAAC AGGAGAGCGC AACGAGGGAG CTTCCCAGGG GGAACGCCT GGTATCTTTA 120
TAGTCCTGTC GGGTTTCGCC ACCTCTGACT TGAGCGTCGA TTTTGTGAT GCTCGTCAGG 180
GGGGCGGAGC CTATGGAAA ACGCCAGCAA CGCGGCTTT TTACGGTTCC TGGCCTTTTG 240
CTGGCCTTTT GCTCACATGT TCTTTCCTGC GTTATCCCCT GATTCTGTGG ATAACCGTAT 300
TACCGCCTTT GAGTGAGCTG ATACCGCTCG CCGCAGCCGA ACGACCGAGC GCAGCGAGTC 360

728

AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT ACGCAAACCG CCTCTCCCCG CGCGTTGGCC	420
GATTCATTAA TGCAGCTGGC ACGACAGGTT TCCCGACTGG AAAGCGGGCA GTGAGCGCAA	480
CGCAATTAAT GTGAGTTAGC TCACTCATTA GGCACCCCAG GCTTTACACT TTATGCTTCC	540
GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA ACAGCTATGA	600
CgtGATTACG AATTCGAGCT CGGTACCCGG AAAATCCAGA AAATGCTTGA AAAAAATCCT	660
AGAAGATGGT ATAATACTAA ATTGTAAGGG TTATCACATA TAACTCAAAA AAAGAAAGAA	720
CAAAAGGAGA GTCAACTAT GGCTTCTAAA GATTTCACG TAGTGGCAGA AACAGGTATT	780
CACGCACGTC CAGCAACATT GTTGTACAA ACTGCTAGCA AATTTGCTTC AGATATCACT	840
CTTGAGTACA AAGGTAAATC AGTTAACCTT AAATCAATTA TGGGTGTAT GAGTCTGGT	900
GTTGGCCAAG GTGCTGACGT AACTATCTCA GCTGAAGGTG CAGATGCAGA TGACGCTATC	960
GCTGCAATCT CAGAAACAAT GGAAAAAGAA GGATTGGCAT AAGGGAAATG ACAGAAATGC	1020
TTAAAGGAAT CGCAGCATCT GACGGTGTG CAGTTGCAAA AGCATATCTA CTCGTTCAGC	1080
CGGATTGTGCT ATTTGAGACT ATTACAGTCG AAGATACAAA CGCAGAAGAA GCTCGCCTTG	1140
ATGCCGCTCT ACAGGCATCA CAAGACGAGC TTTCTGTAT TCGCGAGAAA GCAGTAGGTA	1200
CGCTCGGTGA AGAAGCAGCT CAAGTTTTG ATGCTCACTT AATGGTTCCT GCTGACCCAG	1260
AAATGATCAG CCAATCAAG GAACTATCC GTGCGAAGAA AGTGAATGCA GAAGCAGGTC	1320
TGAAAGAAGT TACAGTATG TTTATCACTA TCTTTGAAGG CATGGAAGAC AACCCATACA	1380
TGCAAGAACG CGCAGCGGAT WCCGCGACG TGACAAAACG TGTATTGGCA AACCTTCTTG	1440
GTAAAAAATT GCCAAACCA GCTTCTATCA ATGAAGAGT GATTGTGATT GCGCATGACT	1500
TGACTCCTTC AGATACAGCT CAATTGGACA AAAACTTTGT AAAAGCTTTT GTAACCAACA	1560
TTGGTGGACG TACAAGCCAC TCAGCTATCA TGGCAGTAC ACTTGAANTT OCTGCTGTAT	1620
TAGGTACAAA TAACATCACT GAAATCGTTA AAGACGGTGA CATCCTTGCT GTTAACGGGA	1680
TCACTGGAGA AGTGATTATC AACCCAACAG ATGAACAAGC GGCAGAATTT AAAGCAGCTG	1740
GTGAAGCCTA TGCGAAACAA AAAGCTGAAT GGGCACTTTT GAAAGATGCT CAAACAGTGA	1800
CTGCTGACGG TAAACACTTC GAGTTGGCTG CTAATATCGG TACTCCAAA GACGTTGAAG	1860
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ATTCTCAAGA CTTCCCACT GAAGATGAGC AGTATGAAGC ATACAAGGCT GTTCTTGAAG	1980
CAATGAACGG TAAACCTGTT GTCGTTCTA CAATGGATAT CGGTGGAGAT AAGGAACTTC	2040
CTTACTTCGA TATGCCTCAC GAAATGAACC CATTCCCTGG ATTCCGTGCT CTTCGTATCT	2100
CTATCTCTGA GACTGGAGAT GCTATGTTCC GCACACAAAT CCGTGCTCTT CTTCGTGCGT	2160

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CTGPTCAGG TCAATTGCGT ATCATGTTCC CAATGGTTGC GCTCTTGAAA GAATTCGGTG	2220
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CGGATAACAT CCAAGTTGGT ATCATGATCG AGATTCCTGC AGCGGCTATG CTTGCAGACC	2340
AATTTGCTAA AGAAGTTGAC TTCTTCTCAA TTGGTACAAA CGACTTGATC CAATATACAA	2400
TGGCAGCAGA CCGTATGAAC GAACAAGTTT CATACCTTTA CCAACCATAC AACCCATCAA	2460
TCCTACGCTT GATTAAACAAT GTGATCAAAG CAGCTCACGC TGAAGGTAAA TGGGCTGGTA	2520
TGTGTGGTGA GATGGCTGGT GACCAACAAG CTGTTCCACT TCTTGTCGGA ATGGGCTTGG	2580
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AGTTGGGACT GTATCAAGCT AGAACGGTTA AGGAAAAATA TCGTGTTCCT TATATAGATG	3120
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AAAGTAATGA CATTGATAGT CTCTTGAAAC AGCTCTACAA ACTGCCTTTG AGTCAACGAC	3900

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CTTGACAAGT TGGATATTTA GGAGTAACT ATTAACCAGT TAAGTAATAG AGAGGAGTTT	2940
CTGCAATTTA GAAATGAATT GCAACTAGAA ATATCAATA GAAAGAGAGT TTGATGAAA	3000
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AGTTGGGACT GTATCAAGCT AGAACGGTTA AGGAAAATAA TCGTGTTTCC TATATAGATG	3120
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GTGGATATGT TATCAAGGTA GATGGAAAAT ACTATGTTTA CCTTAAGGAT GCTGCCACG	3420
CGGATAACGT CCGTACAAAA GAGGAAATCA ATCGACAAA ACAAGAGCAT AGTCAACATC	3480
GTGAAGGTGG AACTCCAAGA AACGATGGTG CTGTTGCCTT GGCACGTTTG CAAGGACGCT	3540
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TGGAAGAACG AATCGCTCGT ATTATTCCCC TTCGTTATCG TTCAAACCAT TGGGTACCAG	4080
ATTCAGAGCC AGAACACCA AGTCCACAAC CGACTCCGGA ACCTAGTCCA GGCCCGCAAC	4140
CTGCACCAAA TCTTAAATA GACTCAAATT CTCTTTGGT TAGTCAGCTG GTACGAAAAG	4200
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GTCTTGCCC TAAGTGTTC TTCCTATGAA CTGCTCGTC ACCAAGCTGG TCAGGTTAAG	5700

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AAAGAGTCTA ATCGAGTTkC TTATATAGAT GGTGATCAGG CTGGTCAAAA GGCAGAAAAC	5760
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ATTACGGATC AAGGTTATGT GACCTCTCAT GGAGACCATT ATCATTACTA TAATGGCAAG	5880
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AAGGATTCAAG ACATTGTCAA TGAAATCAAG GGTGGTTATG TTATCAAGGT AGATGGAAAA	6000
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CCTCATGGTA ACCATTACCA CTTTATCCCT TATGAACAAA TGTCTGAATT GGAAAAACGA	6600
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GAACAACCAA GTCCACAATC GACTCCGAA CCTAGTCCAA GTCCGCAACC TGCACCAAT	6720
CCTCAACCAG CTCCAAGCAA TCCAATTGAT GAGAAATTGG TCAAAGAAGC TGTTCGAAAA	6780
GTAGGCGATG GTTATGTCTT TGAGGAGAAT GGAGTTTCTC GTTATATCCC AGCCAAGGAT	6840
CTTTCAGCAG AAACAGCAGC AGGCATTGAT AGCAAACTGG CCAAGCAGGA AAGTTTATCT	6900
CATAAGCTAG GAGCTAAGAA AACTGACCTC CCATCTAGTG ATCGAGAATT TTACAATAAG	6960
GCTTATGACT TACTAGCAAG AATTACCAA GATTTACTTG ATAATAAAGG TCGACAAGTT	7020
GATTTTGAGG CTTTGGATAA CCTGTTGGAA CGACTCAAGG ATGTCYCAAG TGATAAAGTC	7080
AAGTTAGTGG ATGATATTCT TGCTTCTTA GCTCCGATTC GTCATCCAGA ACGTTTAGGA	7140
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GATGCCTATG TAACTCCACA TATGACCCAT AGCCACTGGA TTAATAAAGA TAGTTTGTCT	7320
GAAGCTGAGA GAGCGGCAGC CCAGGCTTAT GCTAAAGAGA AAGGTTTGAC CCCTCCTCG	7380
ACAGACCATC AGGATTTCAGG AAATACTGAG GCAAAAGGAG CAGAAGCTAT CTACAACCCG	7440

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GTGAAAGCAG CTAAGAAGGT GCCACTTGAT CGTATGCCCTT ACAATCTTCA ATATACTGTA	7500
CAAGTCAAAA ACGGTAGTTT AATCATACCT CATATGACC ATTACCATAA CATCAAATTT	7560
GAGTGGTTTG ACGAAGGCCT TTATGAGGCA CCTAAGGGGT ATACTCTTGA GGATCTTTTG	7620
GCGACTGTCA AGTACTATGT CGAACATCCA AACGAACGTC CGCATTGAGA TAATGGTTTT	7680
GGTAACGCTA GCGACCATGT TCGTAAAAAT AAGGTAGACC AAGACAGTAA ACCTGATGAA	7740
GATAAGGAAC ATGATGAAGT AAGTGAGCCA ACTCACCTG AATCTGATGA AAAAGAGAAT	7800
CACGCTGGTT TAAATCCTTC AGCAGATAAT CTTTATAAAC CAAGCACTGA TACGGAAGAG	7860
ACAGAGGAAG AAGCTGAAGA TACCACAGAT GAGGCTGAAA TTCCTCAAGT AGAGAATTCT	7920
GTTATTAAAC CTAAGATAGC AGATGCGGAG GCCTTGCTAG AAAAAGTAAC AGATCCTAGT	7980
ATTAGACAAA ATGCTATGGA GACATTGACT GGTCTAAAA GTAGTCTTCT TCTCGGAACG	8040
AAAGATAATA ACACTATTTC AGCAGAAGTA GATAGTCTCT TGGCTTTGTT AAAAGAAAGT	8100
CAACCGGCTC CTATACAGTA GTAAAAAGAA TGGAGCATAT TTTATGGAGA AGTAACCTTT	8160
CGTGTACTT CTCTTTTTA GAAAAACGTA ACAGA	8195

(2) INFORMATION FOR SEQ ID NO: 95:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2004 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

TTTACTAAAA GGAAAAAGA ACTGATTTCT CAGTCCTTCA TTAATCTTAT TCCACACTAA	60
ATAGGTATGG GTAAACAGGT TGTGACCTT GGTGAATCTC GACTTCAACG TCTTCGAATT	120
CTTCTACCAT TTCTTGAGCG ATTTCATTGG CAAGTCTTC GCTCCGTCT TCACCTACAT	180
AGAAGGTTAC GATTTCACTG TCTTCATCCA ACATATGTTT CAAGGTTTCA GTCAATGTTT	240
GGTGCAATC AGGTTTGAC ACAAGAATTT TTCCATCCAC CATACCTAAA TTATCGTTTT	300
CATGGATTTT TAAGCCATCG ATCGTTGTAT CACGCACGGC TGTGTGACG CTCCCGCTAA	360
CGACATCGCT AAGAGCAGCT GTCATACGCT CTGGTTTTC TTCAATGGAC TTGCTTGAT	420
CAAAGGCAAG AAGACTTGTG ATACCTTGAG GAAGAGTGGC AGCCTCTACC ACTACCGCTG	480
GTTGCTCCAA AACTTCTGCC GCAGATTGAG CTGCCATGAA GATGTTCTTG TTGTTGGCA	540
AGAAGATGAT GTTACGGGCA TTAACCTGTT CAACAGCCTT GATAAAGTCT TCTGTTGAAG	600
GGTTCATGGT TTGACCGCCT TCGATAACAT AATCCACGCC TTGAGAACAG AAGATATCTG	660

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43. Lysates from frozen brain human tissue were prepared as in (24). Radioactive RT-PCR was performed in a total volume of 50 μ l containing cDNA synthesized from 0.25 μ g RNA, 20 mM Tris-HCl, pH 8.4, 50 mM KCl, 1.5 mM MgCl₂, 0.2 mM dNTPs, 1.7 μ l [α -³²P]CTP, and 0.4 μ M of the primers as follows: hBDNF5', 5'-AGCCA-GAATCGGAACCAACGA-3'; hBDNF3', 5'-GCACACCT-GGGTAGGCCAAG-3'. PCR amplification was carried out for 30 cycles. Each cycle consisted of the following steps: 94°C for 30 s, 57°C for 30 s and 72°C for 30 s. The same amount of each cDNA was also amplified, independently, with SNAP-25 (synaptosomal associated protein 25, a presynaptic membrane-associated protein localized in grown cones, axons and presynaptic terminals) specific primers. SNAP-25 5', 5'-CAATGATGCCGAGAAAAT-3'; SNAP25 3', 5'-GGAATCAGCCT-TCTCCATGA-3'. PCR products were separated by non-denaturing 8% polyacrylamide gel electrophoresis and visualized by autoradiography. BDNF levels were quantified and normalized relative to SNAP-25 levels.
44. V. O. Ona, et al. *Nature* 399, 263 (1999).
45. Total cellular lysates from conditionally immortalized CNS cells (13, 27) were obtained in a buffer containing Tris 50 mM pH 7.4, 5 mM NaCl, Triton X100 1%,

1 mM DTT, 15 mM EGTA supplemented with 1:100 of Protease Inhibitor Cocktail (Sigma). Immunoprecipitates were obtained by incubating the total cellular lysate (from 4×10^6 cells) with Mab2166 (1:1000) following conventional immunoprecipitation protocols and loaded. The blotted proteins were exposed to antibody to Htt Mab2166 (dilution 1:5000; Chemicon, Temecula, CA). RNA was reverse-transcribed into single-stranded cDNA using Superscript II RNase H⁻ Reverse Transcriptase (Life Technologies) as described by the manufacturer. PCR was performed in a total volume of 50 μ l containing 1 μ g cDNA, 20 mM Tris-HCl, pH 8.4, 50 mM KCl, 1.5 mM MgCl₂, 0.2 mM dNTPs, 5% dimethyl sulfoxide (DMSO), 0.4 μ M of Htt-specific primers (5'-CGACCTCGGAAAAGCTGATGAA-3' and 5'-CACACG-GTCTTTCTTGCTACCTGA-3'), 2 U Taq polymerase (Life Technologies). Amplification was carried out for 25 cycles. Each cycle consisted of the following steps: 94°C for 30 s, 56°C for 30 s, and 72°C for 60 s. PCR products were separated by electrophoresis on 2% agarose gel and visualized by staining with ethidium bromide.

46. E. Cattaneo et al., *Trends Neurosci.* 24, 182 (2001).

47. A. C. Bachoud-Levi et al., *Lancet* 356, 1975 (2000).
48. The research described in this manuscript was entirely developed at the Department of Pharmacological Sciences, University of Milano. Supported by grants from the Huntington's Disease Society of America (HDSA, New York), Telethon (Italy #E840) and Ministero dell'Università e della Ricerca Scientifica (Italy, Murst#MM06278849-005), and in part by a grant from the Hereditary Disease Foundation (HDF, Santa Monica) (E.C.) and by funds from Associazione Amici Centro "Dino Ferrari," Milano, Italy (V.S.). T.T. was supported by grants from the Swedish Medical Research Council and Life 2000 Program of the Academy of Finland. We thank R. Molteni for help in setting the RNase Protection Assays. E.C., M.E.M., R.M.F., and M.R.H. are members of the "Coalition for the Cure" (HDSA) and of the "Cure HD Initiative" (HDF).

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Complete Genome Sequence of a Virulent Isolate of *Streptococcus pneumoniae*

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The 2,160,837-base pair genome sequence of an isolate of *Streptococcus pneumoniae*, a Gram-positive pathogen that causes pneumonia, bacteremia, meningitis, and otitis media, contains 2236 predicted coding regions; of these, 1440 (64%) were assigned a biological role. Approximately 5% of the genome is composed of insertion sequences that may contribute to genome rearrangements through uptake of foreign DNA. Extracellular enzyme systems for the metabolism of polysaccharides and hexosamines provide a substantial source of carbon and nitrogen for *S. pneumoniae* and also damage host tissues and facilitate colonization. A motif identified within the signal peptide of proteins is potentially involved in targeting these proteins to the cell surface of low-guanine/cytosine (GC) Gram-positive species. Several surface-exposed proteins that may serve as potential vaccine candidates were identified. Comparative genome hybridization with DNA arrays revealed strain differences in *S. pneumoniae* that could contribute to differences in virulence and antigenicity.

Streptococcus pneumoniae (pneumococcus) has played a pivotal role in the fields of genetics and microbiology. The pioneering studies of Avery, MacLeod, and McCarty in 1944 (1) demonstrated that DNA is the true hereditary material by transforming a noncapsulated, avirulent *S. pneu-*

moniae strain with DNA from a capsulated virulent strain. This work highlighted the importance of the bacterial polysaccharide capsule as a key pathogenicity factor.

As a human pathogen, *S. pneumoniae* is the most common bacterial cause of acute respira-

tory infection and otitis media and is estimated to result in over 3 million deaths in children every year worldwide from pneumonia, bacteremia, or meningitis (2). Even more deaths occur among elderly people, among whom *S. pneumoniae* is the leading cause of community-acquired pneumonia and meningitis (3). Since 1990, the number of penicillin-resistant strains has increased from 1 to 5% to 25 to 80% of isolates, and many strains are now resistant to commonly prescribed antibiotics such as penicillin, macrolides, and fluoroquinolones (4).

The complete genome sequence of a capsular serotype 4 isolate of *S. pneumoniae* [designated TIGR4 (5); TIGR indicates The Institute for Genomic Research] was determined by the random shotgun sequencing strategy (6) (GenBank accession number AE005672; see www.tigr.org/tigr-scripts/CMR2/CMRHomePage.spl). This clinical isolate was taken from the blood of a 30-year-old male patient in Kongsvinger, Norway, and is highly invasive and virulent in a mouse model of infection (7).

The genome consists of a single circular chromosome of 2,160,837 base pairs (bp) with a G + C content of 39.7%. Base pair 1 of the chromosome was assigned within the putative origin of replication. Of the 2236 genes identified (8), 1155 are located on the right of the

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origin of replication, and 916 (79%) of these are transcribed in the same direction as DNA replication; similarly, 1081 genes are on the left of the origin of replication, and 857 (79%) of them

transcribed in the same direction [Fig. 1 and Web fig. 1 (9)]. This type of gene orientation bias appears to be a common feature of low-GC Gram-positive organisms (10).

Although the *S. pneumoniae* genome was reported to contain six ribosomal RNA (rRNA) operons (11), the TIGR4 isolate contains only four rRNA operons. Only 12 of the 58 tRNAs

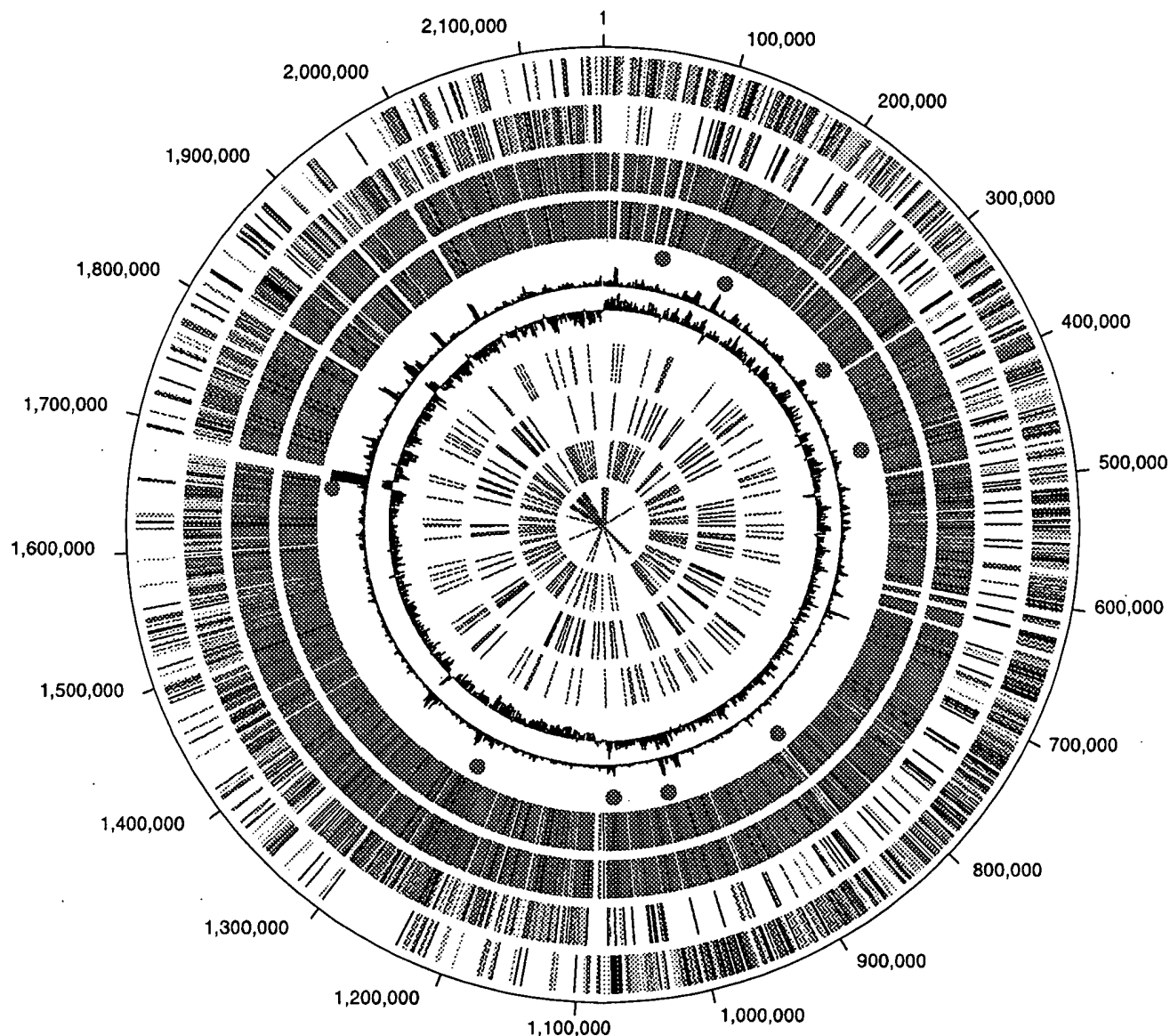
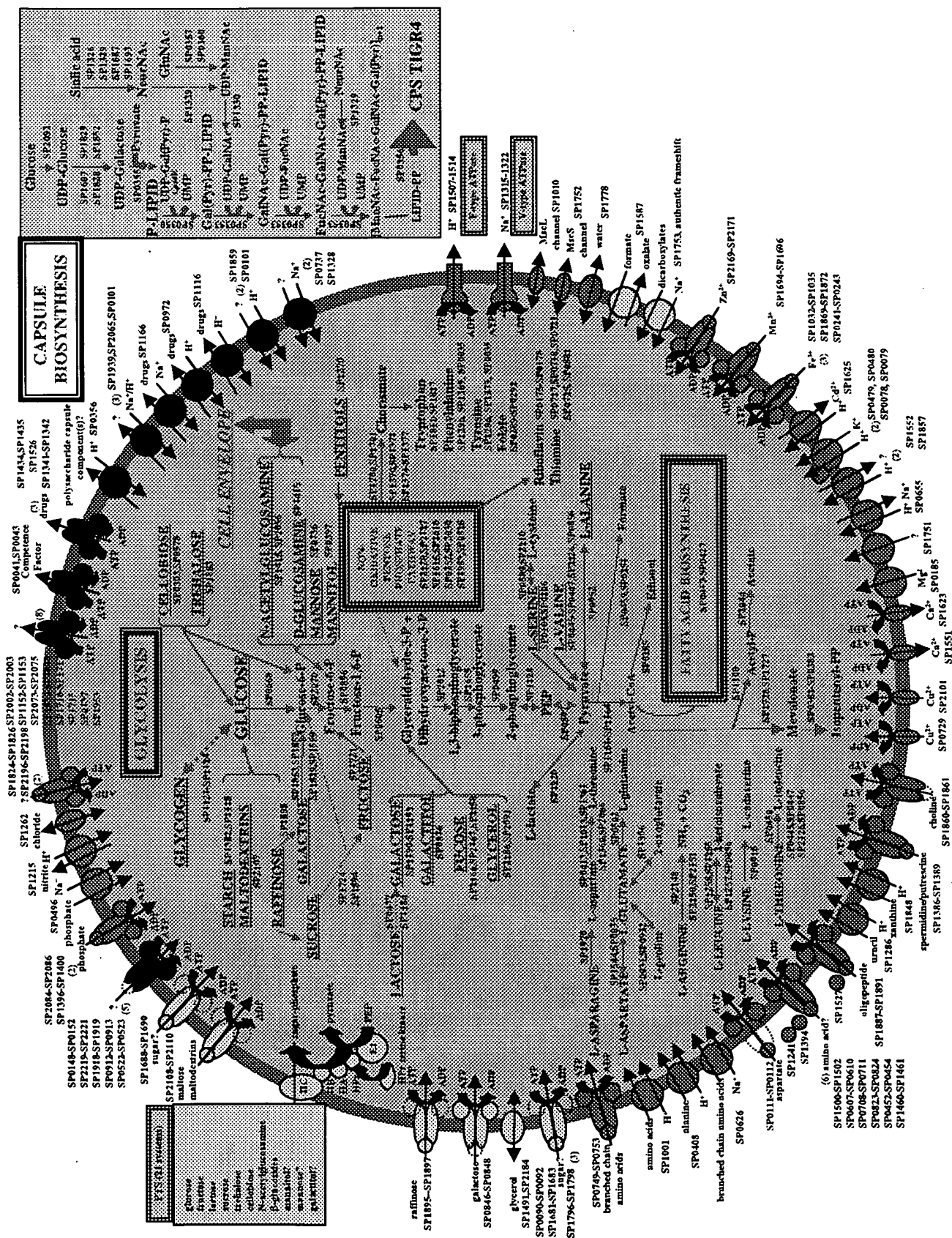


Fig. 1. Circular representation of the *S. pneumoniae* TIGR4 genome and comparative genome hybridizations using microarrays. Comparative genome hybridizations are used to identify genomic differences between the TIGR4 isolate and strains R6 and D39, using a preliminary microarray. Results are displayed on the third and fourth circles. Genes were classified in four groups: (i) gene not present on the array and not analyzed (black) (394 genes, 17% of total); (ii) ortholog present in the test strain (green); (iii) ortholog absent in the test strain (red); and (iv) ambiguous result (blue). The Cy3/Cy5 ratio (TIGR4 signal/test strain) cutoffs for each category were determined subjectively as Cy3/Cy5 = 1.0 to 3.0, green; 3.0 to 10.0, blue; and >10.0, red. There were a number of loci for which hybridization ratios fell between what is expected for gene presence or absence (Cy3/Cy5 ratios between 3.0 to 10.0). Ambiguous results (blue bars) can be explained in at least two ways: (i) The gene may be highly diverged in R6 and/or D39 relative to the TIGR4 isolate. (ii) Alternatively, the gene may be absent in R6 and/or D39 but still be able to produce a hybridization signal, because the TIGR4 isolate gene is a member of a

paralogous gene family or a repetitive element. The outer circle shows predicted coding regions on the plus strand, color-coded by role categories: salmon, amino acid biosynthesis; light blue, biosynthesis of cofactors and prosthetic groups and carriers; light green, cell envelope; red, cellular processes; brown, central intermediary metabolism; yellow, DNA metabolism; green, energy metabolism; purple, fatty acid and phospholipid metabolism; pink, protein fate/synthesis; orange, purines, pyrimidines, nucleosides, and nucleotides; blue, regulatory functions; grey, transcription; teal, transport and binding proteins; black, hypothetical and conserved hypothetical proteins. The second circle shows predicted coding regions on the minus strand, color-coded by role categories. The third circle shows strain R6 genes. The fourth circle shows strain D39 genes. The fifth circle shows an atypical nucleotide composition curve; the nine gene clusters that are absent in strains R6 and D39 are indicated by red bullets. The sixth circle shows the GC-skew curve. The seventh circle shows IS elements. The eighth circle shows RUP elements. The ninth circle shows BOX elements. The tenth circle shows rRNAs in blue, tRNAs in green, and structural RNAs in red.



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are not found adjacent to a rRNA operon [Fig. 1 and Web fig. 1 (9)]. Three structural RNAs were identified: a tRNA-like/mRNA-like (tm) RNA (www.indiana.edu/~truma/), a signal recognition particle RNA (12), and a ribonuclease P RNA (13).

Biological roles were assigned to 1440 (64%) of the predicted proteins according to the classification scheme adapted from Riley (14). Another 359 (16%) predicted proteins matched proteins of unknown function, and the remaining 437 (20%) had no database match. A total of 260 paralogous protein families were identified in the TIGR4 isolate (8), containing 823 predicted proteins (37% of the total).

Comparative genome analysis identified 258 genes in *S. pneumoniae* [Web table 1 (9)] that probably were duplicated after the divergence of this species from other evolutionary lineages for which complete genomes are available (8). Such lineage-specific gene duplications may reveal species-specific adaptations, because gene duplication is frequently accompanied by functional diversification and divergence. These duplications in *S. pneumoniae* include bacteriocin genes, choline-binding proteins, immunoglobulin A (IgA) proteases, immunity proteins, glycosyl transferases, and a large number of hypothetical and conserved hypothetical proteins. Comparison of the complete set of predicted proteins of *S. pneumoniae* with those of other completely sequenced organisms revealed 1219 proteins that are most similar to a protein from another low-GC Gram-positive species (*Lactococcus lactis* has the most with 905) [Web fig. 2 (9)]. Only 105 proteins have no similarity to low-GC Gram-positive proteins [Web table 2 (9)].

Two adjacent genes (SP1467 and SP1468) displayed a high degree of DNA sequence identity (76 and 88%, respectively) between *S. pneumoniae* and *Haemophilus influenzae*. Both pairs of genes, which may be involved in pyridoxine biosynthesis, are more closely related to each other than to orthologs in any other species, which suggests that they were horizontally transferred between these respiratory pathogens.

The *S. pneumoniae* genome is rich in insertion sequences (ISs), which make up ~5% (101,045 bp) of the TIGR4 chromosome [Table 1, Fig. 1, and Web fig. 1 (9)]. IS genes make up

>3.5% (84 out of 2236) of the genes in *S. pneumoniae*, in contrast to other published genomes in which the percentage ranges from 0 to 3% (see www.tigr.org/tigr-scripts/CMR2/CMRHomePage.spl). In addition to IS elements, there are two full-length group II introns and a 1400-bp fragment of the streptococcal conjugative transposon Tn5252. The TIGR4 isolate does not contain any large prophage-like structure or full-length conjugative transposon. The majority of IS elements appear to be non-functional because of insertions, deletions, and/or point mutations (Table 1) that result in frameshifted or degenerated transposase genes. However, programmed frameshifting may allow the expression of several of the frameshifted genes (15). Intact elements are typically families with 98 to 100% nucleotide sequence identity, probably reflecting "waves" of expansion of IS element isotypes. Despite the large number of IS elements, only two genes (encoding hypothetical proteins SP2178/SP2180 and SP0327/SP0329) are disrupted, and one gene (encoding lacX protein SP1194) is truncated by an IS insertion. This suggests selection against insertions into most of the *S. pneumoniae* genes, or some form of editing to remove these insertions, or both. Regarding the latter, it is possible that the complete DNA transformation system identified in the TIGR4 isolate [Web table 3 (9)] may allow conversion of IS disrupted genes by homologous recombination.

Two types of small, dispersed DNA repeats—the RUP and the BOX elements—were identified previously in *S. pneumoniae*. The 107-bp RUP element is thought to act like a nonautonomous insertion sequence that is mobilized by the transposase of IS630-Spn1 (16). The TIGR4 isolate contains 108 RUP elements, which insert preferentially into IS elements. The BOX element is a modular DNA repeat that is composed of three subunits: *boxA*, *boxB* (which can be present in multiple copies), and *boxC* (17). There are 127 BOX elements in the TIGR4 isolate; of these, 115 are intact ($A_1B_0C_1$) and 12 are incomplete. The BOX elements do not appear to be linked to competence or virulence genes, as was previously suggested (17).

There appears to be a system for generating polymorphic type I restriction enzymes in *S. pneumoniae* similar to that found in *Mycoplas-*

ma pulmonis (18). Shotgun sequencing revealed populations of clones from the TIGR4 isolate that were fusions of type I restriction-modification enzyme specificity subunit *hsdS* pseudogenes SP0505 and SP0507 with the nearby intact *hsdS* gene SP0508 [Web fig. 3 (9)]. These rearrangements, which are recombination events between conserved inverted repeats (IRs) within SP0508 and the pseudogenes, might be catalyzed by a nearby integrase (SP0506). Polymerase chain reaction (PCR) on chromosomal DNA using primers inside and outside the *hsdS* genes indicated that the chromosomal region between the IRs was invertible. The specificity subunit may therefore have up to four possible sequences, presumably altering the DNA site recognition of the restriction-modification system and reducing the efficiency of DNA exchange between bacteria in the same clone line.

Streptococcus pneumoniae has the widest substrate utilization range for sugars and substituted nitrogen compounds of the three completed genomes of near-commensal residents of the human upper respiratory tract (*H. influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*). Genome analysis suggests that *S. pneumoniae* possesses pathways for catabolism of pentitols via the pentose phosphate pathway, as well as for cellobiose, fructose, fucose, galactose, galactitol, glucose, glycerol, lactose, mannitol, mannose, raffinose, sucrose, trehalose, and maltosaccharides, which can flow directly into the glycolytic pathway (Fig. 2). Ten amino acids and *N*-acetylglucosamine can potentially be used as nitrogen and carbon sources. Genome analysis also revealed a large number of pathways for the complete or partial synthesis of 14 amino acids and chorismate (Fig. 2).

Streptococcus pneumoniae contains a high percentage of ATP-dependent transporters, as has been seen in other organisms lacking an electron transfer chain (19). *Streptococcus pneumoniae* possesses both a complete F-type proton adenosine triphosphatase (ATPase) and a V-type ATPase that is probably sodium ion-specific. It also has a sodium ion/proton exchanger and several probable sodium ion-driven transporters (Fig. 2), whose activity would be dependent on the establishment of a sodium motive force. Thus, *S. pneumoniae* can probably interconvert the proton gradient, the sodium

Fig. 2. Overview of metabolism and transport in *S. pneumoniae*. Pathways for energy production, metabolism of organic compounds, and capsule biosynthesis are shown. There exist other genes in the capsule biosynthesis locus to which no specific function could be assigned. Transporters are grouped by substrate specificity as follows: inorganic cations (green), inorganic anions (pink), carbohydrates/carboxylates (yellow), amino acids/peptides/amines/purines and pyrimidines (red), and drug efflux and other (black). Question marks indicate uncertainty about the substrate transported. Export or import of solutes is designated by the direction of the arrow through the transporter. The energy-coupling mechanisms of the transporters are also shown: Solutes transported by channel proteins are shown with a double-headed arrow; secondary transporters are shown with two arrowed lines, indicating both the solute and the coupling ion; ATP-driven transporters are

indicated by the ATP hydrolysis reaction; and transporters with an unknown energy coupling mechanism are shown with only a single arrow. Components of transporter systems that function as multisubunit complexes that were not identified are outlined with dotted lines. Where multiple homologous transporters with similar substrate predictions exist, the number of that type of transporter is indicated in parentheses. Systematic gene numbers (SPXXXX) are indicated next to each pathway or transporter; those separated by a dash represent a range of consecutive genes. Details for the PTS transporters are indicated in Web fig. 4 (9). Abbreviations are as follows: ADP, adenosine diphosphate; UMP, uridine monophosphate; UDP, uridine diphosphate; FucNAc, *N*-acetylglucosamine; Gal, galactose; GalNAc, *N*-acetylgalactosamine; GluNAc, *N*-acetylglucosamine; ManNAc, *N*-acetylmannosamine; NeurNAc, *N*-acetylneuraminate; P, phosphate; PP, diphosphate; Pyr, pyruvate.

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ion gradient, and ATP as energy sources, using its F- and V-type ATPases and its sodium ion/proton exchanger. This is somewhat similar to the activity of *Treponema pallidum*, which possesses two V-type ATPases, probably for protons and sodium ions, but no exchanger (20).

Over 30% of the transporters in *S. pneumoniae* were predicted to be sugar transporters (Fig. 2), which is the highest percentage observed to date in any sequenced prokaryote (19). Other completely sequenced respiratory tract organisms, *H. influenzae* and *N. meningitidis*, have a paucity of sugar transporters and are much more reliant on carboxylates and other compounds for their carbon needs. This suggests that *S. pneumoniae* may occupy a distinct microenvironment within the respiratory tract. Host glycoproteins and murein polysaccharides, as well as its own capsular polysaccharides, may be major sources of sugars for *S. pneumoniae*. Reliance on sugar transport and metabolism appears to be a common feature of streptococci, based on their abundance in sugar-rich environments such as the oral cavity (21).

The *S. pneumoniae* sugar transporters primarily consist of phosphoenolpyruvate (PEP)-dependent phosphotransferase system (PTS) transporters and ATP-binding cassette (ABC) transporters. *Streptococcus pneumoniae* has 21 PTS sugar-specific enzyme II complexes with a variety of gene and domain arrangements [Web fig. 4 (9)], more than twice as many as any other sequenced organism relative to genome size, again emphasizing the importance of sugars to the life-style of *S. pneumoniae*. It also possesses single copies of the general PTS enzymes enzyme I and histidine-containing protein (HPr), as well as a HPr serine kinase for regulatory purposes. The *S. pneumoniae* PTS includes systems specific for fructose, glucose, lactose, mannose, mannitol, trehalose, *N*-acetylglucosamine, and sucrose, as well as a variety of PTS systems whose sugar specificities remain to be determined. One PTS system (SP2161 to SP2164) is encoded within a gene cluster including all of the genes necessary for fucose metabolism. *N*-acetylglucosamine is a constituent of the capsule of the TIGR4 isolate, and it is therefore possible that this system may be a PTS for the uptake of *N*-acetylglucosamine or other fucose derivatives. In addition to the PTS, there are seven ABC sugar uptake systems, most of which do not have cytoplasmic ATP-binding components encoded with the other components (Fig. 2).

Streptococcus pneumoniae also possesses a variety of ATP- and ion-driven amino acid transporters, as well as transporters for polyamines, uracil, and xanthine. A single ABC transporter lacking a binding protein was found for choline, an important requirement for the streptococcal cell wall. In contrast to the emphasis on sugar transport, only a single transporter was found for monocarboxylates and one for dicarboxylates. *Streptococcus pneumoniae* has a

relatively limited repertoire of transporters for inorganic anion and cations, although this includes a manganese ABC transporter (SP1648

to SP1650) and a zinc transporter (SP2169 to SP2171), which have been associated with virulence (22), as well as three ferric iron and three

Table 1. *S. pneumoniae* IS families.

IS family*	Name (isotype)	IS size (nt)†	Intact transposase	Truncated or frameshifted	Species with homologous elements‡
IS3	IS3-Spn	1359	0	14	Sp Ec My Sg Ne Ha La Ba
IS5	IS1381-Spn	854–860	0	12	La
IS5	IS1515	861	0	1§	Sp Fr Cy La
IS30	IS1239	1046	0	2	Sp So Cl St Ae Le
IS66	IS66	2484–2498	0	7	
IS110	—	?	0	2	
IS605	IS200	747	2	1	Ec Sa Ye En Cl Ha Vi Wo Th De
IS630	IS630-Spn1	896	0	12	Sp Sy Ne
IS1380	IS1380-Spn	1703	11	1	Ab Sp Ba Xa Kl Sm
ISL3	IS1167	1414–1432	8	14	Sp Sh Sd En La St Le MI
Unknown			0	17	
Total			21	84	

*According to the Mahillon and Chandler classification [J. Mahillon, M. Chandler, *Microbiol. Mol. Biol. Rev.* 62, 725 (1998)]. †Distance between inverted repeats flanking intact or nontruncated IS elements. ‡Species with the most similar elements in GenBank. BlastP hits with an *E* value <10⁻²⁰ were included. Key: Ab, *Acetobacter*; Ae, *Aeromonas*; Ba, *Bacillus*; Cl, *Clostridium*; Cy, *Cyanobacterium*; De, *Deinococcus*; Ec, *E. coli*; En, *Enterococcus*; Fr, *Fremyella*; Ha, *Haemophilus*; Kl, *Klebsiella*; La, *Lactobacillus*; Le, *Leuconostoc*; Mi, *Microcystis*; My, *Mycoplasma*; Ne, *Neisseria*; Sa, *Salmonella*; Sg, *S. agalactiae*; Sd, *S. gordonii*; Sh, *S. thermophilus*; Sm, *Sphingomonas*; So, *S. pyogenes*; Sp, *S. pneumoniae*; St, *Staphylococcus*; Sy, *Synechocystis*; Th, *Thermotoga*; Vi, *Vibrio*; Wo, *Wolbachia*; Xa, *Xanthobacter*; Ye, *Yersinia*. §*S. pneumoniae* element demonstrates functional activity [R. Munoz, R. Lopez, E. Garcia, *J. Bacteriol.* 180, 1381 (1998)].

Table 2. Subset of *S. pneumoniae* genes related to virulence-containing stretches of iterative DNA that could induce phase-variation. Iterative DNA motifs, including homopolymeric tracts, were searched in the TIGR4 genome [see (29)]. The iterative motifs identified in genes related to virulence are displayed. Abbreviations under "location" are as follows: 5', the motif is in the 5' third of the gene; M, the motif is in the middle third; 3', the motif is in the 3' third; P, the motif is within 50 nt upstream of the translation start site. For SP1772, repeats occur in all three parts of the protein.

ORF	Description	Repeat	Location
SP0071	Immunoglobulin A1 protease	(AT) ₄ , (TA) ₄	M, 3'
SP0102	Glycosyl transferase	(G) ₆	M
SP0168	Putative macrolide efflux protein	(TTA) ₄	5'
SP0346	Capsular polysaccharide biosynthesis protein (Cps4A)	(TATT) ₃	5'
SP0349	Capsular polysaccharide biosynthesis protein (Cps4D)	(A) ₈	5'
SP0350	Capsular polysaccharide biosynthesis protein (Cps4E)	(AG) ₄	M
SP0351	Capsular polysaccharide biosynthesis protein (Cps4F)	(A) ₈ , (A) ₉	5', 5'
SP0352	Capsular polysaccharide biosynthesis protein (Cps4G)	(AT) ₄ , (T) ₈	5', M
SP0353	Capsular polysaccharide biosynthesis protein (Cps4H)	(A) ₈	5'
SP0462	Cell wall surface anchor family protein	(GA) ₄	M
SP0664	Putative zinc metalloprotease (ZmpB)	(CAAAA) ₃	5'
SP0689	UDP- <i>N</i> -acetylglucosamine- <i>N</i> -acetylmuramyl-(pentapeptide) pyrophosphoryl-undecaprenol <i>N</i> -acetylglucosamine transferase	(G) ₆ , (G) ₆	5'
SP0907	Putative capsular polysaccharide biosynthesis protein	(G) ₆	5'
SP0966	Adherence and virulence protein A	(A) ₈	5'
SP1267	LicC protein	(ATG) ₄ , (AG) ₄	5', M
SP1272	Putative polysaccharide biosynthesis protein	(CT) ₄ , (CT) ₄	M, 3'
SP1274	LicD2 protein	(A) ₈	5'
SP1492	Cell wall surface anchor family protein	(CT) ₄	3'
SP1693	Neuraminidase A, authentic frameshift	(T) ₈	5'
SP1769	Glycosyl transferase, authentic frameshift	(C) ₉ , (CT) ₄	5', M
SP1772	Cell wall surface anchor family protein	(TCACGCTCGACAA GTGCGTCGGCC) ₅₄₀	
SP1950	Putative bacteriocin formation protein	(T) ₉	P
SP2136	Choline-binding protein (CbpA)	(T) ₈ , (T) ₈	5'
SP2145	Antigen, cell wall surface anchor family	(G) ₆	5'
SP2190	Choline-binding protein A (CbpA)	(T) ₈ , (T) ₈	5', M

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Table 3. *S. pneumoniae* proteins likely to be exposed on the surface, based on computer predictions [see (33)].

ORF	Description	LPxTG*	Choline† binding	Lipoprotein‡	SignalP§	YSIRK	Atypical¶	Repeat#
SP0057	Beta-N-acetylhexosaminidase (StrH)	+			+	+		
SP0069	Choline-binding protein I (Cbpl)		+					
SP0071	Immunoglobulin A1 protease (Iga)	+			+	+		++
SP0082	Cell wall surface anchor family protein	+			+	+		
SP0092	ABC transporter, substrate-binding protein			+	+			
SP0112	Amino acid ABC transporter, periplasmic amino acid-binding protein, putative			+	+			
SP0117	Pneumococcal surface protein A (PspA)		+		+			
SP0148	ABC transporter, substrate-binding protein			+	+			
SP0149	Lipoprotein			+	+			
SP0191	Hypothetical protein			+	+			
SP0198	Hypothetical protein			+	+			
SP0268	Alkaline amylopullulanase, putative	+			+	+		
SP0314	Hyaluronidase	+			+			
SP0368	Cell wall surface anchor family protein, authentic frameshift	+			+	+		
SP0377	Choline-binding protein C (Cbpc)		+		+			
SP0378	Choline-binding protein J (Cbpl)		+		+			
SP0390	Choline-binding protein G (Cbpg)		+					
SP0391	Choline-binding protein F (Cbpf)		+		+			
SP0462	Cell wall surface anchor family protein	+			+			+
SP0463	Cell wall surface anchor family protein	+			+			
SP0464	Cell wall surface anchor family protein	+			+			
SP0468	Sortase, putative			+	+			
SP0498	Endo-beta-N-acetylglucosaminidase, putative	+			+	+		
SP0620	Amino acid ABC transporter, amino acid-binding protein, putative			+	+			
SP0629	Conserved hypothetical protein			+	+			
SP0641	Serine protease, subtilase family	+			+			+++
SP0648	Beta-galactosidase (BgaA)	+			+	+		
SP0659	Thioredoxin family protein			+	+			
SP0664	Zinc metalloprotease ZmpB, putative	+			+		+	+
SP0667	Pneumococcal surface protein, putative		+		+			
SP0771	Peptidyl-prolyl cis-trans isomerase, cyclophilin-type			+	+			
SP0845	Lipoprotein			+	+			
SP0899	Conserved hypothetical protein			+	+			
SP0930	Choline-binding protein E (Cbpe)		+		+			
SP0965	Endo-beta-N-acetylglucosaminidase (LytB)		+		+			
SP0981	Protease maturation protein, putative			+	+			+
SP1000	Thioredoxin family protein			+	+			
SP1002	Adhesion lipoprotein			+	+			
SP1032	Iron-compound ABC transporter, iron compound-binding protein			+	+		+	
SP1154	Immunoglobulin A1 protease (Iga)	+			+	+		
SP1394	Amino acid ABC transporter, amino acid-binding protein			+	+			
SP1400	Phosphate ABC transporter, phosphate-binding protein, putative			+	+			
SP1417	PspC-related protein, degenerate		+					+
SP1492	Cell wall surface anchor family protein	+						+
SP1500	Amino acid ABC transporter, amino acid-binding protein (AatB)			+	+			
SP1527	Oligopeptide ABC transporter, oligopeptide-binding protein (AlbB)			+	+			
SP1573	Lysozyme (LytC)		+		+			+
SP1650	Manganese ABC transporter, manganese-binding adhesion lipoprotein			+	+			
SP1683	Sugar ABC transporter, sugar-binding protein			+	+			
SP1690	ABC transporter, substrate-binding protein			+	+			
SP1772	Cell wall surface anchor family protein	+					+	+(540)
SP1796	ABC transporter, substrate-binding protein			+	+			
SP1826	ABC transporter, substrate-binding protein			+	+			

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Table 3. (Continued)

ORF	Description	LPxTG*	Choline† binding	Lipoprotein‡	SignalP§	YSIRK	Atypical¶	Repeat#
SP1833	Cell wall surface anchor family protein	+				+	+	
SP1870	Iron-compound ABC transporter, permease protein			+	+			
SP1872	Iron-compound ABC transporter, iron-compound binding protein			+	+			+
SP1891	Oligopeptide ABC transporter, oligopeptide-binding protein (AmiA)			+	+			+
SP1897	Sugar ABC transporter, sugar-binding protein (MsmE)			+				
SP1937	Autolysin (LytA)		+					
SP1975	SpolI family protein			+	+			
SP1992	Cell wall surface anchor family protein	+			+			
SP2041	SpolI family protein			+	+			
SP2084	Phosphate ABC transporter, phosphate-binding protein (PstS)			+	+			
SP2108	Maltose/maltodextrin ABC transporter, maltose/maltodextrin-binding protein (MalX)			+	+			
SP2136	Choline-binding protein (PcpA)		+				+	++
SP2169	Zinc ABC transporter, zinc-binding lipoprotein (AdcA)			+	+			
SP2190	Choline-binding protein A (CbpA)	+	+		+	+		++
SP2197	ABC transporter, substrate-binding protein, putative			+	+			
SP2201	Choline-binding protein D (CbpD)		+		+			

*Sortase motif. †Choline-binding motif. ‡Lipid attachment motif. §Signal peptide; a Y-score lower limit of 0.3 was used as the cutoff. ||Signal peptide YSIRK for Gram-positive cell wall-attached proteins. ¶ORFs present in regions of atypical nucleotide composition [see (40)]. #ORFs containing iterative DNA motifs that could induce repeat-associated phase variation; one plus sign is shown per motif (exception: SP1772 contains 540 copies of a 24-nt motif).

phosphate ABC transporters. Overcoming iron and phosphate limitation may also be important for virulence. *Streptococcus pneumoniae* possesses an ABC efflux system involved in competence (SP0042 and SP0043). The characterized macrolide efflux proteins MefE and MefA (23) are absent from the TIGR4 isolate.

Analysis of the genome sequence suggests that extracellular enzyme systems for the metabolism of polysaccharides and hexosamines are important for providing carbon and nitrogen for this organism and may be important for the synthesis of the capsule and the virulence of this species. Enzyme systems based on *N*-acetylglucosaminidases, α - and β -galactosidases, endoglycosidases, hydrolases, hyaluronidases, and neuraminidases are present in *S. pneumoniae*. These enzymes probably enable degradation of host polymers, including mucins, glycolipids, and hyaluronic acid, as well as degradation of the organism's own capsule. These enzymatic activities may serve to increase substrate availability to *S. pneumoniae* by converting larger polymers to products that can be transported into the cell, while at the same time damaging host tissues and facilitating colonization.

Pathogenesis and virulence in *S. pneumoniae* are associated with the inflammation and colonization of host tissues and with bypass of the host immune system [Web table 4 (9)] (24). The polysaccharide capsule is considered to be the primary pneumococcal virulence determinant, allowing for the evasion of the host immune response (25). Although no pathway

has been biochemically characterized for the synthesis of the type 4 capsular polysaccharide, a proposed pathway for capsular biosynthesis derived from the genome analysis is shown in Fig. 2. A 13-gene cluster (SP0346 to SP0360) was identified that is likely to be involved in capsular biosynthesis and secretion. This region of the genome has an atypical nucleotide composition and is flanked by two IS elements on each side. Outside of the IS elements are the *aliA* (also called *plpA*) (SP0366) and *dexB* (SP0342) genes, which also flank the capsule loci in other *S. pneumoniae* strains (26). This gene cluster may not represent the complete pathway for capsular biosynthesis, because several other capsular polysaccharide biosynthesis genes are dispersed elsewhere in the genome. An operon of genes involved in the incorporation of phosphorylcholine into teichoic acid is also present in this genome (SP1267 to SP1274), as are all the genes required for peptidoglycan synthesis.

Phase variation has been described in *S. pneumoniae* and shown to involve variation of multiple cell-surface structures that contribute to the ability of the organism to interact with its host (27). One of the mechanisms involves reversible, high-frequency molecular switching of genes through slippagelike mechanisms at iterative DNA motifs, especially homopolymeric tracts (28). Such motifs were identified in the TIGR4 genome (29), and their location was correlated to predicted genes and their promoters. In total, 397 genes (18%) contain iterative

DNA motifs [Web table 5 (9)] and 25 of these are directly related to virulence (Table 2), including genes from the teichoic acid and capsule pathways that are associated with colony opacity variation (30). In contrast to other pathogenic species, most of the nucleotide repeat-containing genes in *S. pneumoniae* are not frameshifted. This might reflect the presence of general mismatch repair in *S. pneumoniae* (31), a process absent in many pathogens (32).

Sixty-nine proteins that are likely to be exposed on the surface of this organism were identified (Table 3) (33). Genomewide analysis of all predicted signal sequences (34) revealed two discernable clusters. The first cluster contains most of the lipoproteins for which the lipid attachment motif (33) extends beyond the covalently modified cysteine and the membrane-spanning region. This suggests some reuse of lipoprotein signal sequences as evolutionary cassettes. The second cluster, composed of proteins anchored in the cell wall through their sortase motif (33), revealed a previously uncharacterized pentapeptide motif (Y/F)SIRK (35), starting usually at residue 12 (Table 3). A large fraction of the surface proteins of various species of *Streptococcus* and *Staphylococcus* display this motif in their signal peptides. The near-perfect conservation of glycine and serine at the fourth and seventh positions past the pentapeptide, within the predicted transmembrane helix, suggests a specific functional interaction and may reflect a step in cell wall attachment in *S. pneumoniae* and related species.

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Among the newly identified surface-exposed genes are a putative alkaline amylopullulanase (SP0268) and a putative endo- β -N-acetylglucosaminidase (SP0498). These two genes could be involved in the degradation of host polysaccharides. Several cell-wall surface anchor family proteins and lipoproteins are also possibly involved in adherence to host cells. An unusual surface-associated component in this genome is a 4776-amino acid protein (SP1772) that contains 540 imperfect repeats of the amino acid motif SASTSASA (35). This protein is similar to the *Lactobacillus brevis* surface layer protein (36) and to proteins from *S. gordonii* and *S. cristatus*. It is adjacent to seven glycosyl transferases (SP1758, SP1764 to SP1767, SP1770, and SP1771) that could make O-linked glycosylations on the serines in SP1772. This would produce a structure similar to mucins that might also coat the surface of the bacterium or interact with host cellular mucins, although some strains of *S. pneumoniae* have been shown not to interact with mucins (37).

Comparative genome hybridizations on DNA microarrays were performed (38) between the TIGR4 isolate and both the R6 noncapsulated laboratory strain and the closely related D39 serotype 2 capsulated strain (39). Nine gene clusters in the TIGR4 isolate did not hybridize with the other two strains [Fig. 1 and Web table 6 (9)], which suggests that they are absent or significantly divergent in strains R6 and D39. Six of these regions display an atypical nucleotide composition [Fig. 1 and Web table 7 (9)] (40), which suggests that they were horizontally acquired by the TIGR4 isolate. These include the capsule biosynthesis locus (SP0347 to SP0353), the V-type ATPase locus (SP1315 to SP1322), a gene cluster encoding a cell wall surface anchor protein (SP1772) and seven glycosyl transferases, and a putative macrolide efflux protein (SP0168). In addition to these regions, strains R6 and D39 also lack three putative sortases and two sortase motif proteins (SP0463 to SP0468), as well as choline-binding protein I (SP0069) and an IgA1 protease paralog (SP0071). Similar differences in the capsule locus, IgA1 protease, and choline-binding protein were identified by Hakenbeck *et al.* (41) by means of an oligonucleotide-based microarray. The majority of the loci that differ between the three strains are surface-exposed and/or related to pathogenesis, and these differences may contribute to differences in virulence and antigenicity between these strains.

The complete genome sequence of *S. pneumoniae* has revealed new insights into the complexity of its biology and metabolism, particularly with regard to the dual role of extracellular enzyme systems to provide essential nutrients while at the same time facilitating the colonization of host tissues. Recent experimental studies based on the preliminary genome sequence of the TIGR4 isolate have revealed new candidate vaccine targets for this species (42). The avail-

ability of the complete genome sequence will provide additional avenues for followup studies on the basic biology and pathogenicity of *S. pneumoniae*.

References and Notes

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- The TIGR4 isolate was previously referred to as JNR7/87, the label of the clinical isolate [A. L. Bricker, A. Camilli, *FEMS Microbiol. Lett.* **172**, 131 (1999)]; as KNR7/87 [A. de Saizieu *et al.*, *J. Bacteriol.* **182**, 4696 (2000); R. Hakenbeck *et al.*, *Infect. Immun.* **69**, 2477 (2001)]; and as N4 [T. M. Witzmann *et al.*, *Infect. Immun.* **69**, 1593 (2001)]. Midway through the sequencing project, it became evident that one particular bacterial stock was contaminated with *S. gordonii*, because reads from libraries made with DNA derived from this stock were composed entirely of non-*S. pneumoniae* sequences (assessed by using all available *S. pneumoniae* and *S. gordonii* sequences in GenBank) and would not assemble with the *S. pneumoniae* DNA. Because all aspects of the sequencing project are tracked through a relational database [R. D. Fleischmann *et al.*, *Science* **269**, 496 (1995)], the problem was addressed by identifying and removing all the reads from the libraries in question from the project [*S. gordonii* sequences are available on TIGR's Web site www.tigr.org/tdb/s_gordonii.shtml]. The *S. pneumoniae* single-colony isolate that was grown for use in all subsequent libraries was named TIGR4.
- Cloning, sequencing, and assembly were as described [W. C. Nierman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 4136 (2001)]. Four small insert (~1.5 kb) shotgun libraries were constructed in pUC-derived vectors after random mechanical shearing (nebulization) of genomic DNA, and three large insert (~18 kb) shotgun libraries were constructed in λ -DASH II vectors (Stratagene) after partial Sau 3A digestion of genomic DNA. Sequencing of the small insert libraries was achieved at a success rate of 66%, with an average read length of 518 bp. The first library constructed was nonrandom, but improvement of the construction methods provided subsequent random libraries. In contrast, none of the large insert libraries appeared to be completely random. Sequencing of these yielded the following success rates per library: first, 366 nucleotides (nt) average length, with a success rate of 26%; second, 620 nt at 52%; and third, 597 nt at 66%. In the late stages of closure, the newly engineered TIGR vector PHOS2 (a pBR derivative) was used to construct a new large insert (~9 kb) library. Sequencing rates were 508 nt at 48.5% success; these are low values, but the library was substantially more random than the lambda libraries. 40,839 small insert and 3449 large insert end sequences were jointly assembled into 390 contigs larger than 1.5 kb (with 220 sequencing gaps and 170 physical gaps) using TIGR Assembler [G. S. Sutton, O. White, M. D. Adams, A. R. Kerlavage, *Genome Sci. Technol.* **1**, 9 (1995)]. The coverage criteria were that every position required at least double-clone coverage (or sequence from a PCR product amplified from genomic DNA) and either sequence from both strands or with two different sequencing chemistries. The sequence was edited manually with the TIGR Editor, and additional PCR [H. Tettelin, D. Radune, S. Kasif, H. Khouri, S. L. Salzberg, *Genomics* **62**, 500 (1999)] and sequencing reactions were performed to close gaps, improve coverage, and resolve sequence ambiguities. Particularly difficult regions, including SP1772, which contains 540 copies of a 24-bp imperfect repeat, were covered by transposon-assisted sequencing (New England Biolabs pGPS Transposon Kit) and mapping of transposon insertions before assembly.
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- Open reading frames (ORFs) likely to encode proteins were predicted by Glimmer [S. L. Salzberg, A. L. Delcher, S. Kasif, O. White, *Nucleic Acids Res.* **26**, 544 (1998); A. L. Delcher, D. Harmon, S. Kasif, O. White, S. L. Salzberg, *Nucleic Acids Res.* **27**, 4636 (1999)]. This program, based on interpolated Markov models, was trained with ORFs larger than 600 bp from the genomic sequence, as well as with the *S. pneumoniae* genes available in GenBank. All predicted proteins larger than 30 amino acids were searched against a nonredundant protein database, as previously described [R. D. Fleischmann *et al.*, *Science* **269**, 496 (1995)]. Frameshifts and point mutations were detected and corrected where appropriate. Remaining frameshifts and point mutations are considered to be authentic and were annotated as "authentic frameshift" or "authentic point mutation." Protein membrane-spanning domains were identified by TopPred [M. G. Claros, G. von Heijne, *Comput. Appl. Biosci.* **10**, 685 (1994)]. The 5' regions of each ORF were inspected to define initiation codons using homologies, position of ribosomal binding sites, and transcriptional terminators. Two sets of hidden Markov models were used to determine ORF membership in families and superfamilies: pfam v5.5 [A. Bateman *et al.*, *Nucleic Acids Res.* **28**, 263 (2000)] and TIGRFAMs 1.0 [D. H. Haft *et al.*, *Nucleic Acids Res.* **29**, 41 (2001)]. Pfam v5.5 hidden Markov models were also used with a constraint of a minimum of two hits to find repeated domains within proteins and mask them. Domain-based paralogous families were then built by performing all-versus-all searches on the remaining protein sequences, using a modified version of a previously described method [W. C. Nierman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 4136 (2001)]. The extent of potential lineage-specific gene duplications in this genome was estimated by identification of ORFs that are more similar to other ORFs within the TIGR4 genome than to ORFs from other complete genomes, including those of plasmids, organelles, and phages. All ORFs were searched with FASTA3 against all ORFs from the complete genomes, and matches with a FASTA *p* value of 10^{-5} were considered significant.
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REPEATS program [G. Benson, M. S. Waterman, *Nucleic Acids Res.* 22, 4828 (1994)]. The minimum length of homopolymeric tracts was set at eight for A and T and at six for G and C; four tandem copies of di- and trinucleotides; and three copies of tetra-, penta-, and hexanucleotides. Heptanucleotides and above were not found in three or more copies, except for the imperfect repeats in SP1772. The ratio of the observed frequency of homopolymeric tracts to their expected frequency was determined by means of Markov chain analysis, as described [N. J. Saunders et al., *Mol. Microbiol.* 37, 207 (2000)]. It revealed that G or C tracts of 8 bp and A or T tracts of 10 and 11 bp are slightly overrepresented.

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33. Putative choline-binding motifs [J. L. Garcia, A. R. Sanchez-Beato, F. J. Medrano, R. Lopez, in *Streptococcus pneumoniae—Molecular Biology and Mechanisms of Disease*, A. Tomasz, Ed. (Mary Ann Liebert, Larchmont, NY, 2000), pp. 231–244] were identified using Pfam hidden Markov model (HMM) PF01473 [A. Bateman et al., *Nucleic Acids Res.* 28, 263 (2000)]. LPXTG-type Gram-positive anchor regions [M. J. Pallen, A. C. Lam, M. Antonio, K. Dunbar, *Trends Microbiol.* 9, 97 (2001)] were detected by Pfam HMM PF00746 and by a new HMM built with HMMER 2.1.1 [S. R. Eddy, *Bioinformatics* 14, 755 (1998)] from a new, curated alignment of the surrounding region in *S. pneumoniae*. Candidate lipoprotein signal peptides [S. Hayashi, H. C. Wu, *J. Bioenerg. Biomembr.* 22, 451 (1990)] were flagged by NH₂-terminal exact matches to the pattern (DERK)(6)–[LVFMFWSTAG](2)–[LVFMFYTAGGQ]–[AGS]–C (35), culled of hypothetical proteins and cytosolic proteins, aligned manually, and used to generate a new HMM. Proteins matching both the HMM and the regular expression are predicted lipoproteins. Putative signal peptides were identified with SignalP [H. Nielsen, J. Engelbrecht, S. Brunak, G. von Heijne, *Protein Eng.* 10, 1 (1997)].
34. The NH₂-terminal regions of all proteins predicted to have signal sequences were collected for clustering and alignment with ClustalW and were scrutinized. A HMM based on an edited alignment of 40-residue segments around the (Y/F)SIRK motif found several hundred hits to a nonredundant amino acid database. A more general motif, based on the larger family of YSIRK proteins, is (Y/F)(S/A)(I/L)(R/K)(R/K)xxxGxxS (35).
35. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
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38. This method is used to identify genomic differences between the TIGR4 strain and strains R6 and D39. All the predicted genes from the TIGR4 strain were amplified by PCR and arrayed on glass microscope slides as previously described [S. Peterson, R. T. Cline, H. Tettelin, V. Sharov, D. A. Morrison, *J. Bacteriol.* 182, 6192 (2000)]. Genomic DNA for comparative genome hybridization studies was labeled according to protocols provided by J. DeRisi (www.microarrays.org/pdfs/GenomicDNALabel_B.pdf), except that genomic DNA was not digested or sheared before labeling. Arrays were scanned with a GenePix 4000B scanner from Axon (Union City, CA), and individual hybridization signals were quantitated with TIGR SPOTFINDER [P. Hegde et al., *Biotechniques* 29, 548 (2000)].
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40. Regions of atypical nucleotide composition were identified by the χ^2 analysis. The distribution of all 64 trinucleotides (trimers) was computed for the complete genome in all six reading frames, followed by the trimer distribution in 2000-bp windows. Windows overlapped by 1500 bp. For each window, the χ^2 statistic on the difference between its trimer content and that of the whole genome was computed. The most atypical regions, with a score of 600 and above, were considered in this analysis.

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42. T. M. Wlzemann et al., *Infect. Immun.* 69, 1593 (2001).
43. We thank M. Heaney, J. Scott, M. Holmes, V. Sapiro, B. Lee, and B. Vincent for software and database support at TIGR; M. Ermolaeva and M. Perlea for specific computer analyses; the TIGR faculty and sequencing core for expert advice and assistance; I. Aaberge (National Institute of Public Health, Oslo, Norway) for providing the initial

clinical isolate labeled JNR.7/87; and G. Zysk and A. Polissi for sharing specific sequence data not deposited in GenBank. Supported in part by the National Institutes of Allergy and Infectious Diseases (grant R01 AI40645-01A1) and the Merck Genome Research Institute (grant MGRI72).

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NPAS2: An Analog of Clock Operative in the Mammalian Forebrain

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Neuronal PAS domain protein 2 (NPAS2) is a transcription factor expressed primarily in the mammalian forebrain. NPAS2 is highly related in primary amino acid sequence to Clock, a transcription factor expressed in the suprachiasmatic nucleus that heterodimerizes with BMAL1 and regulates circadian rhythm. To investigate the biological role of NPAS2, we prepared a neuroblastoma cell line capable of conditional induction of the NPAS2:BMAL1 heterodimer and identified putative target genes by representational difference analysis, DNA microarrays, and Northern blotting. Coincidence of NPAS2 and BMAL1 activated transcription of the endogenous *Per1*, *Per2*, and *Cry1* genes, which encode negatively activating components of the circadian regulatory apparatus, and repressed transcription of the endogenous *BMAL1* gene. Analysis of the frontal cortex of wild-type mice kept in a 24-hour light-dark cycle revealed that *Per1*, *Per2*, and *Cry1* mRNA levels were elevated during darkness and reduced during light, whereas *BMAL1* mRNA displayed the opposite pattern. In situ hybridization assays of mice kept in constant darkness revealed that *Per2* mRNA abundance did not oscillate as a function of the circadian cycle in NPAS2-deficient mice. Thus, NPAS2 likely functions as part of a molecular clock operative in the mammalian forebrain.

Locomotor activity, body temperature, endocrine hormones, and metabolic rate fluctuate cyclically with a period of 24 hours. The regulatory apparatus that controls circadian rhythm consists of a transcriptional feedback cycle that is evolutionarily conserved in a wide variety of metazoans (1). In mammals, the activating arm of this cycle is executed by a heterodimeric transcription factor composed of the *Clock* and *BMAL1* gene products (2). The *Clock*:*BMAL1* heterodimer binds directly to regulatory sequences of the genes comprising the negative arm of the transcriptional feedback cycle. The negative components of the regulatory apparatus include three period (*Per*) genes and two cryptochrome (*Cry*) genes (3–11), whose products function in a poorly understood manner to inactivate the *Clock*:*BMAL1* heterodimer. The duration of *Per* and *Cry* activity may be modified by a serine-threonine kinase variously termed casein kinase 1 ϵ or Tau in mam-

mals and Doubletime in flies (12–14). In the absence of entraining influences, this regulatory apparatus oscillates rhythmically at or near the 24-hour light-dark cycle (i.e., 12 hours light, 12 hours dark). Entrainment derived from light, food, temperature, and metabolic activity can advance or delay the central regulatory apparatus such that it is properly adapted to the summation of these external zeitgebers.

The master pacemaker of circadian rhythm resides in the suprachiasmatic nucleus (SCN), a small group of neurons located at the base of the optic chiasma within the central nervous system (15). Classical transplantation experiments have demonstrated that the SCN is necessary and sufficient to specify circadian rhythm (16, 17). Surprisingly, the same molecular clock is operative in sites peripheral to the SCN (11, 18), including cultured mammalian cells of non-neural origin (19).

Neuronal PAS domain protein 2 (NPAS2, also termed MOP4) is a member of the basic helix-loop-helix (bHLH)–PAS domain family of transcription factors. The gene encoding NPAS2 is expressed in a stereotypic pattern of brain nuclei located within the mammalian forebrain (20, 21). Upon positional cloning of

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CLUSTAL W (1.74) multiple sequence alignment

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tr|Q6WNQ5|Q6WNQ5_STRPN      -----CAYALNQHRSQENK-DNNR
tr|Q8CWR4|Q8CWR4_STRR6      -MNQIYLRKEERMKINKKYLGSVATLVLSVCAYELGLHQQTVK-ENNR
tr|Q8DPQ2|Q8DPQ2_STRR6      MQL EISNRKRVS MKINKKYL VGSAAALILSVCSYELGLYQARTVK-ENNR
tr|Q9AG74|Q9AG74_STRPN      -----MKINKKYL VGSAAALILSVCSYELGLYQARTVK-ENNR
tr|Q9AHT9|Q9AHT9_STRPN      -----MKINKKYL VGSAAALILSVCSYELGLYQARTVK-ENNR
tr|Q8DQ08|Q8DQ08_STRR6      -----MKINKKYLGSVAVLALSVCSYELGRHQAGQVKKESNR
                                *: * . : : * . : *

tr|Q6WNQ5|Q6WNQ5_STRPN      VSYVDGSQSSQKSENLTDPQVSQKEGIQAEQIVIKITDQGYVTSHGDHYH
tr|Q8CWR4|Q8CWR4_STRR6      VSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYH
tr|Q8DPQ2|Q8DPQ2_STRR6      VSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYH
tr|Q9AG74|Q9AG74_STRPN      VSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYH
tr|Q9AHT9|Q9AHT9_STRPN      VSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYH
tr|Q8DQ08|Q8DQ08_STRR6      VSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYH
                                ***:*. *: *:*****:*. :*:*****:*****

tr|Q6WNQ5|Q6WNQ5_STRPN      YYNGKVPYDALFSEELLMKDPNYQLKDADIVNEVKGGYIIKVDGKYYVYL
tr|Q8CWR4|Q8CWR4_STRR6      YYNGKVPYDAI ISEELLMKDPNYQLKDEDI ISEIKGGYVIKVDGKYYVYL
tr|Q8DPQ2|Q8DPQ2_STRR6      YYNGKVPYDAI FSEELLMKDPNYKLKDEDIVNEVKGGYVIKVDGKYYVYL
tr|Q9AG74|Q9AG74_STRPN      YYNGKVPYDAI ISEELLMKDPNYQLKDEDI ISEIKGGYVIKVDGKYYVYL
tr|Q9AHT9|Q9AHT9_STRPN      YYNGKVPYDAI ISEELLMKDPNYKLKDEDIVNEVKGGYVIKVDGKYYVYL
tr|Q8DQ08|Q8DQ08_STRR6      YYNGKVPYDAI ISEELLMKDPNYQLKDSDIVNEIKGGYVIKVDGKYYVYL
                                *****:*. *****:*** *: *:*****:*****

tr|Q6WNQ5|Q6WNQ5_STRPN      KDAAHADNVRTKDEINRQKQEHVKDNE----KVNSNVAVARSQGRYTND
tr|Q8CWR4|Q8CWR4_STRR6      KDAAHADNVRTKEEINRQKQEH SQHREGGT PRNDGAVALARSQGRYTDD
tr|Q8DPQ2|Q8DPQ2_STRR6      KDAAHADNVRTKEEINRQKQEH SQHREGGT PRNDGAVALARSQGRYTDD
tr|Q9AG74|Q9AG74_STRPN      KDAAHADNVRTKEEINRQKQEH SQHREGGT PRNDGAVALARSQGRYTDD
tr|Q9AHT9|Q9AHT9_STRPN      KDAAHADNVRTKEEINRQKQEH SQHREGGT PRNDGAVALARSQGRYTDD
tr|Q8DQ08|Q8DQ08_STRR6      KDAAHADNIRTKEEIKRQKQERSHNHN---SRADNAVAAARAQGRYTDD
                                *****:***:*. *****: :. : : * * *:*****:

tr|Q6WNQ5|Q6WNQ5_STRPN      GYVENPADIIEDTGNAYIVPHRGHYHYIPKSDL SASELAAAKAHLAKG--
tr|Q8CWR4|Q8CWR4_STRR6      GYIFNASDIIEDTGDAYIVPHGDHYHYIPKNEL SASELAAAKAFLSGRGN
tr|Q8DPQ2|Q8DPQ2_STRR6      GYIFNASDIIEDTGDAYIVPHGDHYHYIPKNEL SASELAAAEAFLSGRGN
tr|Q9AG74|Q9AG74_STRPN      GYIFNASDIIEDTGDAYIVPHGDHYHYIPKNEL SASELAAAKAFLSGRGN
tr|Q9AHT9|Q9AHT9_STRPN      GYIFNASDIIEDTGDAYIVPHGDHYHYIPKNEL SASELAAAEAFLSGRGN
tr|Q8DQ08|Q8DQ08_STRR6      GYIFNASDIIEDTGDAYIVPHGDHYHYIPKSDL SASELAAQAQYWNGK--
                                **:*. :*****:***** .*****:*****:*. *:

tr|Q6WNQ5|Q6WNQ5_STRPN      -----NMQP-SQLSYSSTASD---NNTQSVAKGSTSKPANKSEN
tr|Q8CWR4|Q8CWR4_STRR6      LSN SRTYRRQNSDNTSRTNWVPSVSNPGTTNTNTSNNSNTNSQASQSN
tr|Q8DPQ2|Q8DPQ2_STRR6      LSN SRTYRRQNSDNTSRTNWVPSVSNPGTTNTNTSNNSNTNSQASQSN
tr|Q9AG74|Q9AG74_STRPN      LSN SRTYRRQNSDNTSRTNWVPSVSNPGTTNTNTSNNSNTNSQASQSN
tr|Q9AHT9|Q9AHT9_STRPN      LSN SRTYRRQNSDNTSRTNWVPSVSNPGTTNTNTSNNSNTNSQASQSN
tr|Q8DQ08|Q8DQ08_STRR6      -----QGSRPSSSSSHNANPAQPR LSENHNLTVTPTYHQN-QGENI
                                . * . . : : . : . * : : :

tr|Q6WNQ5|Q6WNQ5_STRPN      QSL LKELYDSPAQRYS ESDGLVFDPAKII SRTPNGVAIPHGDHYHFIPY
tr|Q8CWR4|Q8CWR4_STRR6      DSLLKQLYKLPLSQRHVESDGLIFDPAQITSRTANGVAVPHGDHYHFIPY
tr|Q8DPQ2|Q8DPQ2_STRR6      DSLLKQLYKLPLSQRHVESDGLVFDPAQITSRTANGVAVPHGDHYHFIPY
tr|Q9AG74|Q9AG74_STRPN      DSLLKQLYKLPLSQRHVESDGLIFDPAQITSRTANGVAVPHGDHYHFIPY
tr|Q9AHT9|Q9AHT9_STRPN      DSLLKQLYKLPLSQRHVESDGLVFDPAQITSRTANGVAVPHGDHYHFIPY
tr|Q8DQ08|Q8DQ08_STRR6      SLLRELYAKPLSERHVESDGLIFDPAQITSRTANGVAVPHGDHYHFIPY
                                .***:*. * :*: *****:*****: * * * . * . :*****

tr|Q6WNQ5|Q6WNQ5_STRPN      SKLSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSK

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tr Q8CWR4 Q8CWR4_STRR6	SQLSPLEEKLARIIPLYRSNHWPDSRP-EQSPSQSTPEPSPSPPQAPN
tr Q8DPQ2 Q8DPQ2_STRR6	SQMSELEERIARIIPLYRSNHWPDSRP-EQSPSQPTPEPSPGPQAPN
tr Q9AG74 Q9AG74_STRPN	SQLSPLEEKLARIIPLYRSNHWPDSRP-EQSPSQSTPEPSPSPPQAPN
tr Q9AHT9 Q9AHT9_STRPN	SQMSELEERIARIIPLYRSNHWPDSRP-EQSPSQPTPEPSPGPQAPN
tr Q8DQ08 Q8DQ08_STRR6	SQLSPLEEKLARIIPLYRSNHWPDSRP-EQSPSQSTPEPSPSPPQAPN
	*.: * *.: *.: *.: .. .: * * *.: *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	ELSSASDGYIFNPKDIVEETATAYIVRHGDHFHYIPKSNQIQPTLPNNS
tr Q8CWR4 Q8CWR4_STRR6	PQPAPS-----NP--IDEKLVKEAVRKVG DG--YVFEENG VPR--YIPAKD
tr Q8DPQ2 Q8DPQ2_STRR6	-LKIDS-----N-----SSLVSQLVRKVGE G--YVFEEKGISR--YVFAKD
tr Q9AG74 Q9AG74_STRPN	PQPAPS-----NP--IDEKLVKEAVRKVG DG--YVFEENG VPR--YIPAKD
tr Q9AHT9 Q9AHT9_STRPN	-LKIDS-----N-----SSLVSQLVRKVGE G--YVFEEKGISR--YVFAKD
tr Q8DQ08 Q8DQ08_STRR6	PQPAPS-----NP--IDEKLVKEAVRKVG DG--YVFEENG VPR--YIPAKD
	* * .. .: *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	LATPSPSLPINPGTSHEKHEEDGYGFDANRIIAEDES GFVMSHGDNHNYF
tr Q8CWR4 Q8CWR4_STRR6	LSAET---AAGIDSKLAKQESLSHKLGA KK---TD-----LPSSDREFYN
tr Q8DPQ2 Q8DPQ2_STRR6	LPSET---VKNLESKLSKQESVSHTLTAKK---EN-----VAPRDQEFYD
tr Q9AG74 Q9AG74_STRPN	LSAET---AAGIDSKLAKQESLSHKLGA KK---TD-----LPSSDREFYN
tr Q9AHT9 Q9AHT9_STRPN	LPSET---VKNLESKLSKQESVSHTLTAKK---EN-----VAPRDQEFYD
tr Q8DQ08 Q8DQ08_STRR6	LSAET---AAGIDSKLAKQESLSHKLGA KK---TD-----LPSSDREFYN
	*.: *.: *.: *.: *.: *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	FKKDLTTEEQIKAAQKHLEEVKTS HNGLDLSLSHEQDYPSNAKEMKDLDDKK
tr Q8CWR4 Q8CWR4_STRR6	KAYDLLARIHQD LLDN-KGRQVD FEALDNLLERLKDVS SSKVKVLVD---D
tr Q8DPQ2 Q8DPQ2_STRR6	KAYNLLTEAHKALFEN-KGRNSDFQALDKLLERLNDESTNKEK LVD---D
tr Q9AG74 Q9AG74_STRPN	KAYDLLARIHQD LLDN-KGRQVD FEALDNLLERLKDVS SSKVKVLVD---D
tr Q9AHT9 Q9AHT9_STRPN	KAYNLLTEAHKALFXN-KGRNSDFQALDKLLERLNDESTNKEK LVD---D
tr Q8DQ08 Q8DQ08_STRR6	KAYDLLARIHQD LLDN-KGRQVD FEALDNLLERLKDVS SSKVKVLVD---D
	: * .: : : : : : *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	IEEKIAGIMKQYGVKRESIVVNKEKNAIIPHG DHHHADPIDEHKPVGIG
tr Q8CWR4 Q8CWR4_STRR6	ILAF LAPIRHP---ER---LGKPNAQIT YTD-----DEIQVAKLAGKY
tr Q8DPQ2 Q8DPQ2_STRR6	LLAF LAPITHP---ER---LGKPNSQIE YTE-----DEVRIAQLADKY
tr Q9AG74 Q9AG74_STRPN	ILAF LAPIRHP---ER---LGKPNAQIT YTD-----DEIQVAKLAGKY
tr Q9AHT9 Q9AHT9_STRPN	LLAF LAPITHP---ER---LGKPNSQIE YTE-----DEVRIAQLADKY
tr Q8DQ08 Q8DQ08_STRR6	ILAF LAPIRHP---ER---LGKPNAQIT YTD-----DEIQVAKLAGKY
	: : * * : : * : *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	HSHSNYELFKPEEGVAKKEGNKVYTGEELTNV VNLKLNSTFNNQNFTLAN
tr Q8CWR4 Q8CWR4_STRR6	TTEDGY-IFDPRD-ITSDEGD-AYVTPHMT HSHWIKKDS-LSEAERAAAQ
tr Q8DPQ2 Q8DPQ2_STRR6	TTSDGY-IFDEHD-IISDEGD-AYVTPHMG HSHWIKKDS-LSDKEKVAAQ
tr Q9AG74 Q9AG74_STRPN	TTEDGY-IFDPRD-ITSDEGD-AYVTPHMT HSHWIKKDS-LSEAERAAAQ
tr Q9AHT9 Q9AHT9_STRPN	TTSDGY-IFDEHD-IISDEGD-AYVTPHMG HSHWIKKDS-LSDKEKVAAQ
tr Q8DQ08 Q8DQ08_STRR6	TTEDGY-IFDPRD-ITSDEGD-AYVTPHMT HSHWIKKDS-LSEAERAAAQ
	: .. * *.: *.: *.: *.: *.: *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	GQKRVSFSFPPELEKKLGINMLVKLITPDGKVLEK VSGKVFEGGVGNIAN
tr Q8CWR4 Q8CWR4_STRR6	AYAKEKGLTPPSTDH QDSGN-----TEAKGAEAIYNRVKAA-----KK
tr Q8DPQ2 Q8DPQ2_STRR6	AYTKEKGILPPSPDADVKAN-----PTGDSAAAIYNRVKGE-----KR
tr Q9AG74 Q9AG74_STRPN	AYAKEKGLTPPSTDH QDSGN-----TEAKGAEAIYNRVKAA-----KK
tr Q9AHT9 Q9AHT9_STRPN	AYTKEKGILPPSPDADVKAN-----PTGDSAAAIYNRVKGE-----KR
tr Q8DQ08 Q8DQ08_STRR6	AYAKEKGLTPPSTDH QDSGN-----TEAKGAEAIYNRVKAA-----KK
	. : . *.: *.: *.: *.: *.: *.: *.: *.: *
tr Q6WNQ5 Q6WNQ5_STRPN	FELDQPYLPQGTFKYTIASKDYPEVSYDGTFTVPTS LAYKMASQTIIFYPF
tr Q8CWR4 Q8CWR4_STRR6	VPLDR--MP--YNLQYTVEVK-----NGSLIIP---HYDHYHNIKFEWF
tr Q8DPQ2 Q8DPQ2_STRR6	IPLVR--LP--YMVEHTVEVK-----NGNLIIP---HKDHYHNIKFAWF
tr Q9AG74 Q9AG74_STRPN	VPLDR--MP--YNLQYTVEVK-----NGSLIIP---HYDHYHNIKFEWF
tr Q9AHT9 Q9AHT9_STRPN	IPLVR--LP--YMVEHTVEVK-----NGNLIIP---HKDHYHNIKFAWF

```

tr|Q8DQ08|Q8DQ08_STRR6      VPLDR--MP-YNLQYTVEVK-----NGSLIIP---HYDHYHNIKFEWF
. * : : * . : : * * : * : : * : * *

tr|Q6WNQ5|Q6WNQ5_STRPN      HAGDTYLRVNPQFAVPKGTDALVRVFDEFHGNAYLENNYKVGEIKLPIPK
tr|Q8CWR4|Q8CWR4_STRR6      ---DEGLYEAPKGYSLDLLATVKYYVE-HPNERPHSDNGFGNASDHVQR
tr|Q8DPQ2|Q8DPQ2_STRR6      ---DDHTYKAPNGYTLLEDLFATIKYYVE-HPDERPHSDNGWGNASEHVLG
tr|Q9AG74|Q9AG74_STRPN      ---DEGLYEAPKGYSLDLLATVKYYVE-HPNERPHSDNGFGNASDHVQR
tr|Q9AHT9|Q9AHT9_STRPN      ---DDHTYKAPNGYTLLEDLFATIKYYVE-HPDERPHSDNGWGNASEHVLG
tr|Q8DQ08|Q8DQ08_STRR6      ---DEGLYEAPKGYSLDLLATVKYYVE-HPNERPHSDNGFGNASDHVQR
                                *      *:      :. * : : * * :      :. : * : . :

tr|Q6WNQ5|Q6WNQ5_STRPN      LNQGTTTRTAGNKIPVTFMANAYLDNQSTYIVEVPILEKENQTD-----
tr|Q8CWR4|Q8CWR4_STRR6      NKNQGADTNQTEKPNEEKQPTEKPEEETPRECKPQSEKPE-----
tr|Q8DPQ2|Q8DPQ2_STRR6      KKDHSDEPNKNFKADEE-----
tr|Q9AG74|Q9AG74_STRPN      NKNQGADTNQTEKPNEEKQPTEKPEEETPRECKPQSEKPE-----
tr|Q9AHT9|Q9AHT9_STRPN      KKDHSDEPNKNFKADEE-----
tr|Q8DQ08|Q8DQ08_STRR6      NKNQGADTNQTEKPNEEKQPTEKPEEDKEHDEVSEPTHPESDEKENHVGL
                                : :      .      .

tr|Q6WNQ5|Q6WNQ5_STRPN      -----KPSILPQFKRNKAQENSKFDEKVVEPKTSEKVEKEKLSETGN
tr|Q8CWR4|Q8CWR4_STRR6      -P-----KP-----TEEPEESPEES--PEESEPQVETEKVKEKLREA--
tr|Q8DPQ2|Q8DPQ2_STRR6      -----P-----VEET--PAEPEVPQVETEKVEAQLKEA--
tr|Q9AG74|Q9AG74_STRPN      -P-----KP-----TEEPEESPEES--PEESEPQVETEKVKEKLREA--
tr|Q9AHT9|Q9AHT9_STRPN      -----P-----VEET--PAEPEVPQVETEKVEAQLKEA--
tr|Q8DQ08|Q8DQ08_STRR6      NPSADNLYKPSTDTETEETEEA--EDT--TDEAEIPQVEHSVINAKIAEA--
                                *      *:      : * * : . . : : : * :

tr|Q6WNQ5|Q6WNQ5_STRPN      STSNSTLEEVPVTPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSGE
tr|Q8CWR4|Q8CWR4_STRR6      ---EDLLGKIQ--NPIIKSNAKETLT-GLK-NNLLFGTQDNNTIMAEA--
tr|Q8DPQ2|Q8DPQ2_STRR6      ---EVLLAKVT--DSSLKANATETLA-GLR-NNLTLQIMDNNSIMAEA--
tr|Q9AG74|Q9AG74_STRPN      ---EDLLGKIQ--NPIIKSNAKETLT-GLK-NNLLFGTQDNNTIMAEA--
tr|Q9AHT9|Q9AHT9_STRPN      ---EVLLAKVT--DSSLKANATETLA-GLR-NNLTLQIMDNNSIMAEA--
tr|Q8DQ08|Q8DQ08_STRR6      ---EALLEKVT--DSSIRQNAVETLT-GLK-SSLLLGTKDNNTISAEV--
                                : * : : . . * : : * : : . : : . :

tr|Q6WNQ5|Q6WNQ5_STRPN      VIKKNMADFTGEAPQNGENKPSSENGKVSTGTVENQPTENKPADSLPEAP
tr|Q8CWR4|Q8CWR4_STRR6      --EKLLALLKESK-----
tr|Q8DPQ2|Q8DPQ2_STRR6      --EKLLALLKGSNPSSVSKEKIN-----
tr|Q9AG74|Q9AG74_STRPN      --EKLLALLKESK-----
tr|Q9AHT9|Q9AHT9_STRPN      --EKLLALLKGSNPSSVSKEKIN-----
tr|Q8DQ08|Q8DQ08_STRR6      --DSLLALLKESQPTPIQ-----
                                . . : * . . .

tr|Q6WNQ5|Q6WNQ5_STRPN      NEKPVKPENSTDNGMLNPEGNVGSDPMLDPALEEAPAVDPVQEKLEKFTA
tr|Q8CWR4|Q8CWR4_STRR6      -----
tr|Q8DPQ2|Q8DPQ2_STRR6      -----
tr|Q9AG74|Q9AG74_STRPN      -----
tr|Q9AHT9|Q9AHT9_STRPN      -----
tr|Q8DQ08|Q8DQ08_STRR6      -----

tr|Q6WNQ5|Q6WNQ5_STRPN      SYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA
tr|Q8CWR4|Q8CWR4_STRR6      -----
tr|Q8DPQ2|Q8DPQ2_STRR6      -----
tr|Q9AG74|Q9AG74_STRPN      -----
tr|Q9AHT9|Q9AHT9_STRPN      -----
tr|Q8DQ08|Q8DQ08_STRR6      -----

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FileUp

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 Name: tr|Q8DPQ2|Q8DPQ2_STRRR6 oo Len: 1086 Check: 7473 Weight: 0.100
 Name: tr|Q9AG74|Q9AG74_STRPN oo Len: 1086 Check: 1008 Weight: 0.100
 Name: tr|Q9AHT9|Q9AHT9_STRPN oo Len: 1086 Check: 5019 Weight: 0.100
 Name: tr|Q8DQ08|Q8DQ08_STRRR6 oo Len: 1086 Check: 3058 Weight: 0.100

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tr|Q6WNQ5|Q6WNQ5_STRPNCAYALNQHR SQENK.DNNR
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 tr|Q9AG74|Q9AG74_STRPNMKINKKYL VGSAAALILS VCSYELGLYQ ARTVK.ENNR
 tr|Q9AHT9|Q9AHT9_STRPNMKINKKYL VGSAAALILS VCSYELGLYQ ARTVK.ENNR
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tr|Q6WNQ5|Q6WNQ5_STRPN VSYVDGSQSS QKSENLTDPQ VSQKEGIQAE QIVIKITDQG YVTSHGDHYH
 tr|Q8CWR4|Q8CWR4_STRRR6 VSYIDGKQAT QKTENLTPDE VSKREGINAE QIVIKITDQG YVTSHGDHYH
 tr|Q8DPQ2|Q8DPQ2_STRRR6 VSYIDGKQAT QKTENLTPDE VSKREGINAE QIVIKITDQG YVTSHGDHYH
 tr|Q9AG74|Q9AG74_STRPN VSYIDGKQAT QKTENLTPDE VSKREGINAE QIVIKITDQG YVTSHGDHYH
 tr|Q9AHT9|Q9AHT9_STRPN VSYIDGKQAT QKTENLTPDE VSKREGINAE QIVIKITDQG YVTSHGDHYH
 tr|Q8DQ08|Q8DQ08_STRRR6 VSYIDGDQAG QKAENLTPDE VSKREGINAE QIVIKITDQG YVTSHGDHYH

tr|Q6WNQ5|Q6WNQ5_STRPN YYNGKVPYDA LFSEELLMKD PNYQLKDADI VNEVKGGYII KVDGKYYVYL
 tr|Q8CWR4|Q8CWR4_STRRR6 YYNGKVPYDA IISEELLMKD PNYQLKDEDI ISEIKGGYVI KVDGKYYVYL
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 tr|Q9AG74|Q9AG74_STRPN YYNGKVPYDA IISEELLMKD PNYQLKDEDI ISEIKGGYVI KVDGKYYVYL
 tr|Q9AHT9|Q9AHT9_STRPN YYNGKVPYDA IISEELLMKD PNYKLKDEDI VNEVKGGYVI KVDGKYYVYL
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tr|Q6WNQ5|Q6WNQ5_STRPN KDAAHADNVR TKDEINRQKQ EHVKDNE... .KVNSNVAVA RSQGRYTTND
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tr|Q6WNQ5|Q6WNQ5_STRPN GYVFNPADII EDTGNAYIVP HRGHYHYIPK SDLSASELAA AKAHLAGK..
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 tr|Q9AG74|Q9AG74_STRPN GYIFNASDII EDTGDAYIVP HGDHYHYIPK NELSASELAA AKAFLSGRGN
 tr|Q9AHT9|Q9AHT9_STRPN GYIFNASDII EDTGDAYIVP HGDHYHYIPK NELSASELAA AEAFLSGRGN
 tr|Q8DQ08|Q8DQ08_STRRR6 GYIFNASDII EDTGDAYIVP HGDHYHYIPK SDLSASELAA AQAYWNGK..

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 tr|Q8DPQ2|Q8DPQ2_STRRR6 LNSRITYRRQ NSDNTSRTNW VPSVSNPGTT NTNTSNNST NSQASQSN

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tr Q8DQ08 Q8DQ08_STRR6Q	GSRPSSSSSH	NANPAQPRLS	ENHNLTVTPT	YHQN.QGENI
tr Q6WNQ5 Q6WNQ5_STRPN	QSLKELYDS	PSAQRYSERD	GLVFDPAKII	SRTPNGVAIP	HGDHYHFIPY
tr Q8CWR4 Q8CWR4_STRR6	DSLLKQLYKL	PLSQRHVESD	GLIFDPAQIT	SRTANGVAVP	HGDHYHFIPY
tr Q8DPQ2 Q8DPQ2_STRR6	DSLLKQLYKL	PLSQRHVESD	GLVFDPAQIT	SRTANGVAVP	HGDHYHFIPY
tr Q9AG74 Q9AG74_STRPN	DSLLKQLYKL	PLSQRHVESD	GLIFDPAQIT	SRTANGVAVP	HGDHYHFIPY
tr Q9AHT9 Q9AHT9_STRPN	DSLLKQLYKL	PLSQRHVESD	GLVFDPAQIT	SRTANGVAVP	HGDHYHFIPY
tr Q8DQ08 Q8DQ08_STRR6	SSLLRELYAK	PLSERHVESD	GLIFDPAQIT	SRTANGVAVP	HGDHYHFIPY
tr Q6WNQ5 Q6WNQ5_STRPN	SKLSALEEKI	ARMVPISGTG	STVSTNAKPN	EVVSSLGSL	SNPSSLTTSK
tr Q8CWR4 Q8CWR4_STRR6	SQLSPLEEK	ARIIPLYRS	NHWVPDSRP	EQPSPQSTPE	PSPSPQAPN
tr Q8DPQ2 Q8DPQ2_STRR6	SQMSELEER	ARIIPLYRS	NHWVPDSRP	EQPSPQSTPE	PSPSPQAPN
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tr Q9AHT9 Q9AHT9_STRPN	SQMSELEER	ARIIPLYRS	NHWVPDSRP	EQPSPQSTPE	PSPSPQAPN
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tr Q8CWR4 Q8CWR4_STRR6	PQPAPS....	.NP..IDEKL	VKEAVRKVD	G..YVFEENG	VPR.YIPAKD
tr Q8DPQ2 Q8DPQ2_STRR6	.LKIDS....	.N....SSL	VSQVLRKVG	G..YVFEENG	ISR.YVFAKD
tr Q9AG74 Q9AG74_STRPN	PQPAPS....	.NP..IDEKL	VKEAVRKVD	G..YVFEENG	VPR.YIPAKD
tr Q9AHT9 Q9AHT9_STRPN	.LKIDS....	.N....SSL	VSQVLRKVG	G..YVFEENG	ISR.YVFAKD
tr Q8DQ08 Q8DQ08_STRR6	PQPAPS....	.NP..IDEKL	VKEAVRKVD	G..YVFEENG	VPR.YIPAKD
tr Q6WNQ5 Q6WNQ5_STRPN	LATPSPSLPI	NPGTSHEKHE	EDGYGFDANR	IIAEDESGFV	MSHGDHNNHYF
tr Q8CWR4 Q8CWR4_STRR6	LSAET...AA	GIDSKLAKQE	SLSHKLGAKK	...TD.....	LPSSDREFYN
tr Q8DPQ2 Q8DPQ2_STRR6	LPSET...VK	NLESKLSKQE	SVSHTLTAKK	...EN.....	VAPRDQEFYD
tr Q9AG74 Q9AG74_STRPN	LSAET...AA	GIDSKLAKQE	SLSHKLGAKK	...TD.....	LPSSDREFYN
tr Q9AHT9 Q9AHT9_STRPN	LPSET...VK	NLESKLSKQE	SVSHTLTAKK	...EN.....	VAPRDQEFYD
tr Q8DQ08 Q8DQ08_STRR6	LSAET...AA	GIDSKLAKQE	SLSHKLGAKK	...TD.....	LPSSDREFYN
tr Q6WNQ5 Q6WNQ5_STRPN	FKKDLTEEQI	KAAQKHLEEV	KTSHNGLDL	SSHEQDYPSN	AKEMKDLDKK
tr Q8CWR4 Q8CWR4_STRR6	KAYDLLARIH	QDLLDN.KGR	QVDFEALDNL	LERLKDVS	KVKLVD...D
tr Q8DPQ2 Q8DPQ2_STRR6	KAYNLLTEAH	KALFEN.KGR	NSDFQALDKL	LERLNDESTN	KEKLVD...D
tr Q9AG74 Q9AG74_STRPN	KAYDLLARIH	QDLLDN.KGR	QVDFEALDNL	LERLKDVS	KVKLVD...D
tr Q9AHT9 Q9AHT9_STRPN	KAYNLLTEAH	KALFXN.KGR	NSDFQALDKL	LERLNDESTN	KEKLVD...D
tr Q8DQ08 Q8DQ08_STRR6	KAYDLLARIH	QDLLDN.KGR	QVDFEALDNL	LERLKDVS	KVKLVD...D
tr Q6WNQ5 Q6WNQ5_STRPN	IEEKIAGIMK	QYGVKRESIV	VNKEKNAIY	PHGDHHHADP	IDEHKPVGIG
tr Q8CWR4 Q8CWR4_STRR6	ILAFLAPIRH	P...ER....	LGKPNQITY	TD.....DE	IQVAKLAGKY
tr Q8DPQ2 Q8DPQ2_STRR6	LLAFLAPITH	P...ER....	LGKPNQIEY	TE.....DE	VRIAQLADKY
tr Q9AG74 Q9AG74_STRPN	ILAFLAPIRH	P...ER....	LGKPNQITY	TD.....DE	IQVAKLAGKY
tr Q9AHT9 Q9AHT9_STRPN	LLAFLAPITH	P...ER....	LGKPNQIEY	TE.....DE	VRIAQLADKY
tr Q8DQ08 Q8DQ08_STRR6	ILAFLAPIRH	P...ER....	LGKPNQITY	TD.....DE	IQVAKLAGKY
tr Q6WNQ5 Q6WNQ5_STRPN	HSHSNYELFK	PEEGVAKKEG	NKVTGEELT	NVVNLLKNST	FNNQNFTLAN
tr Q8CWR4 Q8CWR4_STRR6	TTEDGY.IFD	PRD.ITSDEG	D.AYVTPHMT	HSHWIKKDS	LSEAERAAQ
tr Q8DPQ2 Q8DPQ2_STRR6	TTSDGY.IFD	EHD.IISDEG	D.AYVTPHMG	HSHWIKKDS	LSDKEKVAAQ
tr Q9AG74 Q9AG74_STRPN	TTEDGY.IFD	PRD.ITSDEG	D.AYVTPHMT	HSHWIKKDS	LSEAERAAQ
tr Q9AHT9 Q9AHT9_STRPN	TTSDGY.IFD	EHD.IISDEG	D.AYVTPHMG	HSHWIKKDS	LSDKEKVAAQ
tr Q8DQ08 Q8DQ08_STRR6	TTEDGY.IFD	PRD.ITSDEG	D.AYVTPHMT	HSHWIKKDS	LSEAERAAQ

tr Q6WNQ5 Q6WNQ5_STRPN	GQKRVSFSFP	PELEKKLGIN	MLVKLITPDG	KVLEKVSQKV	FGEGVGNIAN
tr Q8CWR4 Q8CWR4_STRR6	AYAKEKGLTP	PSTDHQDSGNTEA	KGAEAIYNRV	KAA.....KK
tr Q8DPQ2 Q8DPQ2_STRR6	AYTKEKGILP	PSPDADVKANPTG	DSAAAIYNRV	KGE.....KR
tr Q9AG74 Q9AG74_STRPN	AYAKEKGLTP	PSTDHQDSGNTEA	KGAEAIYNRV	KAA.....KK
tr Q9AHT9 Q9AHT9_STRPN	AYTKEKGILP	PSPDADVKANPTG	DSAAAIYNRV	KGE.....KR
tr Q8DQ08 Q8DQ08_STRR6	AYAKEKGLTP	PSTDHQDSGNTEA	KGAEAIYNRV	KAA.....KK

tr Q6WNQ5 Q6WNQ5_STRPN	FELDQPYLPG	QTFKYTIASK	DYPEVSYDGT	FTVPTSLAYK	MASQTIFYPF
tr Q8CWR4 Q8CWR4_STRR6	VPLDR..MP.	YNLQYTVVEVKNGS	LIIP...HYD	HYHNIKFEWF
tr Q8DPQ2 Q8DPQ2_STRR6	IPLVR..LP.	YMVEHTVEVKNGN	LIIP...HKD	HYHNIKFAWF
tr Q9AG74 Q9AG74_STRPN	VPLDR..MP.	YNLQYTVVEVKNGS	LIIP...HYD	HYHNIKFEWF
tr Q9AHT9 Q9AHT9_STRPN	IPLVR..LP.	YMVEHTVEVKNGN	LIIP...HKD	HYHNIKFAWF
tr Q8DQ08 Q8DQ08_STRR6	VPLDR..MP.	YNLQYTVVEVKNGS	LIIP...HYD	HYHNIKFEWF

tr Q6WNQ5 Q6WNQ5_STRPN	HAGDTYLRVN	PQFAVPKGT	ALVRVFDEFH	GNAYLENNYK	VGEIKLPIPK
tr Q8CWR4 Q8CWR4_STRR6	...DEGLYEA	PKGYSLEDLL	ATVKYYVE.H	PNRPHSDNG	FGNASDHVQR
tr Q8DPQ2 Q8DPQ2_STRR6	...DDHTYKA	PNGYTLEDLF	ATIKYYVE.H	PDERPHSNDG	WGNASEHVLG
tr Q9AG74 Q9AG74_STRPN	...DEGLYEA	PKGYSLEDLL	ATVKYYVE.H	PNRPHSDNG	FGNASDHVQR
tr Q9AHT9 Q9AHT9_STRPN	...DDHTYKA	PNGYTLEDLF	ATIKYYVE.H	PDERPHSNDG	WGNASEHVLG
tr Q8DQ08 Q8DQ08_STRR6	...DEGLYEA	PKGYSLEDLL	ATVKYYVE.H	PNRPHSDNG	FGNASDHVQR

tr Q6WNQ5 Q6WNQ5_STRPN	LNQGTTRTAG	NKIPVTFMAN	AYLDNQSTYI	VEVPILEKEN	QTD.....
tr Q8CWR4 Q8CWR4_STRR6	NKNGQADTNQ	TEKPNEEKPQ	TEKPEEETPR	EEKPQSEKPE	S.....
tr Q8DPQ2 Q8DPQ2_STRR6	KKDHSEDPNK	NFKADEE...
tr Q9AG74 Q9AG74_STRPN	NKNGQADTNQ	TEKPNEEKPQ	TEKPEEETPR	EEKPQSEKPE	S.....
tr Q9AHT9 Q9AHT9_STRPN	KKDHSEDPNK	NFKADEE...
tr Q8DQ08 Q8DQ08_STRR6	NKNGQADTNQ	TEKPNEEKPQ	TEKPEEDKEH	DEVSEPTHE	SDEKENHVGL

tr Q6WNQ5 Q6WNQ5_STRPNKP	SILPQFKRKN	AQENSKFDEK	VEEPTSEKV	EKEKLSETGN
tr Q8CWR4 Q8CWR4_STRR6	.P.....KP	...TEEPSEE	SPEES..PEE	SEEPQVETEK	VKEKLREA..
tr Q8DPQ2 Q8DPQ2_STRR6PVEET..PAE	PEVPQVETEK	VEAQLKEA..
tr Q9AG74 Q9AG74_STRPN	.P.....KP	...TEEPSEE	SPEES..PEE	SEEPQVETEK	VKEKLREA..
tr Q9AHT9 Q9AHT9_STRPNPVEET..PAE	PEVPQVETEK	VEAQLKEA..
tr Q8DQ08 Q8DQ08_STRR6	NPSADNLYKP	STDTEETEE	A.EDT..TDE	AEIPQVEHSV	INAKIAEA..

tr Q6WNQ5 Q6WNQ5_STRPN	STSNSTLEE	PTVDPVQEKV	AKFAESYGMK	LENVLFNMDG	TIELYLPSGE
tr Q8CWR4 Q8CWR4_STRR6	...EDLLGKI	Q..NPIIKSN	AKETLT.GLK	.NNLLFGTQD	NNTIMAEA..
tr Q8DPQ2 Q8DPQ2_STRR6	...EVLLAKV	T..DSSLKAN	ATETLA.GLR	.NNLTLQIMD	NNSIMAEA..
tr Q9AG74 Q9AG74_STRPN	...EDLLGKI	Q..NPIIKSN	AKETLT.GLK	.NNLLFGTQD	NNTIMAEA..
tr Q9AHT9 Q9AHT9_STRPN	...EVLLAKV	T..DSSLKAN	ATETLA.GLR	.NNLTLQIMD	NNSIMAEA..
tr Q8DQ08 Q8DQ08_STRR6	...EALLEKV	T..DSSIRQN	AVETLT.GLK	.SSLLLGTKD	NNTISAEV..

tr Q6WNQ5 Q6WNQ5_STRPN	VIKKNMADFT	GEAPQNGEN	KPSENGKVST	GTVENQPTEN	KPADSLPEAP
tr Q8CWR4 Q8CWR4_STRR6	..EKLLALLK	ESK.....
tr Q8DPQ2 Q8DPQ2_STRR6	..EKLLALLK	GSPSSVSKE	KIN.....
tr Q9AG74 Q9AG74_STRPN	..EKLLALLK	ESK.....
tr Q9AHT9 Q9AHT9_STRPN	..EKLLALLK	GSPSSVSKE	KIN.....
tr Q8DQ08 Q8DQ08_STRR6	..DSLLALLK	ESQPTPIQ..

tr Q6WNQ5 Q6WNQ5_STRPN	NEKPVKPENS	TDNGMLNPEG	NVGSDPMLDP	ALEEAPAVDP	VQEKLEKFTA
tr Q8CWR4 Q8CWR4_STRR6
tr Q8DPQ2 Q8DPQ2_STRR6

tr Q9AG74 Q9AG74_STRPN
tr Q9AHT9 Q9AHT9_STRPN
tr Q8DQ08 Q8DQ08_STRR6

tr Q6WNQ5 Q6WNQ5_STRPN	SYGLGLDSVI	FNMDGTIELR	LPSGEVIKKN	LSDLIA
tr Q8CWR4 Q8CWR4_STRR6
tr Q8DPQ2 Q8DPQ2_STRR6
tr Q9AG74 Q9AG74_STRPN
tr Q9AHT9 Q9AHT9_STRPN
tr Q8DQ08 Q8DQ08_STRR6

tr Q6WNQ7 Surface protein BVH-3 [bvh-3] [Streptococcus
Q6WNQ7_STRPN pneumoniae]

1039
AA
align

Score = 1134 bits (2933), Expect = 0.0
Identities = 565/567 (99%), Positives = 565/567 (99%)

Johnston
PH3
BVH3

Query: 1 LTEEQIKAAQKHLEEVKTSNGLDSLSSHEQDYPSNAKEMKDLDKKIEEKIAGIMKQYGV 60
LTEEQIKAAQKHLEEVKTSNGLDSLSSHEQDYF NAKEMEDLUKKIEEKIAGIMKQYGV
Sbjct: 473 LTEEQIKAAQKHLEEVKTSNGLDSLSSHEQDYPGNAKEMKDLDKKIEEKIAGIMKQYGV 532

Query: 61 KRESIVVNKEKNAIITYPHGDHHHADPIDEHKPVGIGHSHSNYELFKPEEGVAKKEGNKVY 120
KRESIVVNKEKNAIITYPHGDHHHADPIDEHKPVGIGHSHSNYELFKPEEGVAKKEGNKVY
Sbjct: 533 KRESIVVNKEKNAIITYPHGDHHHADPIDEHKPVGIGHSHSNYELFKPEEGVAKKEGNKVY 592

Query: 121 TGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPELEKKLGINMLVKLITPDGKVLE 180
TGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPELEKKLGINMLVKLITPDGKVLE
Sbjct: 593 TGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPELEKKLGINMLVKLITPDGKVLE 652

Query: 181 KVSGKVFGEVGNIANFELDQPYLPGQTFKYTIASKDYPEVSYDGTFTVPTSLAYKMASQ 240
KVSGKVFGEVGNIANFELDQPYLPGQTFKYTIASKDYPEVSYDGTFTVPTSLAYKMASQ
Sbjct: 653 KVSGKVFGEVGNIANFELDQPYLPGQTFKYTIASKDYPEVSYDGTFTVPTSLAYKMASQ 712

Query: 241 TIFYPFHAGD TYLRVNPQFAVPKGT DALVRVDFEFHGNAYLENNYKVGEIKLPIPKLNQG 300
TIFYPFHAGD TYLRVNPQFAVPKGT DALVRVDFEFHGNAYLENNYKVGEIKLPIPKLNQG
Sbjct: 713 TIFYPFHAGD TYLRVNPQFAVPKGT DALVRVDFEFHGNAYLENNYKVGEIKLPIPKLNQG 772

Query: 301 TTRTAGNKIPVTFMANAYLDNQSTYIVEVPILEKENQTDKPSILPQFKRNKAQENLKLDE 360
TTRTAGNKIPVTFMANAYLDNQSTYIVEVPILEKENQTDKPSILPQFKRNKAQEN KLDE
Sbjct: 773 TTRTAGNKIPVTFMANAYLDNQSTYIVEVPILEKENQTDKPSILPQFKRNKAQENSKLDE 832

Query: 361 KVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPTVDPVQEKVAKFAESYGMKLENVLFNMD 420
KVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPTVDPVQEKVAKFAESYGMKLENVLFNMD
Sbjct: 833 KVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPTVDPVQEKVAKFAESYGMKLENVLFNMD 892

Query: 421 GTIELYLPSGEVIKKNMADFTGEAPQNGENKPSSENGKVSTGTVENQPTENKPADSLPEA 480
GTIELYLPSGEVIKKNMADFTGEAPQNGENKPSSENGKVSTGTVENQPTENKPADSLPEA
Sbjct: 893 GTIELYLPSGEVIKKNMADFTGEAPQNGENKPSSENGKVSTGTVENQPTENKPADSLPEA 952

Query: 481 PNEKPVKPENSTDNGMLNPEGNVGSDPMLDPALEEAPAVDPVQEKLEKFTASYGLGLDSV 540
PNEKPVKPENSTDNGMLNPEGNVGSDPMLDPALEEAPAVDPVQEKLEKFTASYGLGLDSV
Sbjct: 953 PNEKPVKPENSTDNGMLNPEGNVGSDPMLDPALEEAPAVDPVQEKLEKFTASYGLGLDSV 1012

Query: 541 IFNMDGTIELRLPSGEVIKKNLSDLIA 567
IFNMDGTIELRLPSGEVIKKNLSDLIA
Sbjct: 1013 IFNMDGTIELRLPSGEVIKKNLSDLIA 1039

Q6WNQ5 Surface protein BVH-3 (Fragment) [bvh-3] [Streptococcus 1019
Q6WNQ5_STRPN pneumoniae] AA
align

Score = 1504 bits (3893), Expect = 0.0
Identities = 743/779 (95%), Positives = 743/779 (95%)

phTE
BVH-3

Query: 1 AYALNQHRSQENKDNRRVSYVDGSQSSQKSENLTDPQVSQKEGIQAEQIVIKITDQGYVT 60
AYALNQHRSQENKDNRRVSYVDGSQSSQKSENLTDPQVSQKEGIQAEQIVIKITDQGYVT
Sbjct: 2 AYALNQHRSQENKDNRRVSYVDGSQSSQKSENLTDPQVSQKEGIQAEQIVIKITDQGYVT 80

Query: 61 SHGDHYHYINGKVPYDALFSEELLMKDPNYQLKDADIVNEVKGGYIIKVDGKYYVYLKDA 120
SHGDHYHYINGKVPYDALFSEELLMKDPNYQLKDADIVNEVKGGYIIKVDGKYYVYLKDA
Sbjct: 62 SHGDHYHYINGKVPYDALFSEELLMKDPNYQLKDADIVNEVKGGYIIKVDGKYYVYLKDA 140

Query: 121 AHADNVRTKDEINRQKQEHVKDNEKVNNSVAVARSQGRYTTNDGYVFNPAIIEDTGNAY 180
AHADNVRTKDEINRQKQEHVKDNEKVNNSVAVARSQGRYTTNDGYVFNPAIIEDTGNAY
Sbjct: 122 AHADNVRTKDEINRQKQEHVKDNEKVNNSVAVARSQGRYTTNDGYVFNPAIIEDTGNAY 200

Query: 181 IVPHGHHYHYIPXXXXXXXXXXXXXXXXXXXXNMQPSQLSYSSTASDNNTQSVAKGSTSKP 240
IVPH GHYHYIP NMQPSQLSYSSTASDNNTQSVAKGSTSKP
Sbjct: 182 IVPHRGHYHYIPKSDLSASELAAKAHLAKNMQPSQLSYSSTASDNNTQSVAKGSTSKP 260

Query: 241 ANKSENLSLLKELYDSPSAQRYSES DGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSKL 300
ANKSENLSLLKELYDSPSAQRYSES DGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSKL
Sbjct: 242 ANKSENLSLLKELYDSPSAQRYSES DGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSKL 320

Query: 301 SALEEKIARMVPISGTGSTVSTNAKPNEVVXXXXXXXXXXXXXXXXXXXXKELSSASDGYIFNP 360
SALEEKIARMVPISGTGSTVSTNAKPNEVV KELSSASDGYIFNP
Sbjct: 302 SALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFNP 380

Query: 361 KDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEEDG 420
KDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEEDG
Sbjct: 362 KDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEEDG 440

Query: 421 YGFDANRIIAEDES GFVMSHGDHNYFFKKDLTEEQIKAAQKHLEEVKTS HNGLDLSSH 480
YGFDANRIIAEDES GFVMSHGDHNYFFKKDLTEEQIKAAQKHLEEVKTS HNGLDLSSH
Sbjct: 422 YGFDANRIIAEDES GFVMSHGDHNYFFKKDLTEEQIKAAQKHLEEVKTS HNGLDLSSH 500

Query: 481 EQDYPSNAKEMKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDE 540
EQDYPSNAKEMKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDE
Sbjct: 482 EQDYPSNAKEMKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDE 560

Query: 541 HKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQK 600
HKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQK
Sbjct: 542 HKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQK 620

Query: 601 RVSFSFPPELEKKLGINMLVKLITPDGKVLEKVS GKVFGEGVGNIANFELDQPYLPQGTF 660
RVSFSFPPELEKKLGINMLVKLITPDGKVLEKVS GKVFGEGVGNIANFELDQPYLPQGTF
Sbjct: 602 RVSFSFPPELEKKLGINMLVKLITPDGKVLEKVS GKVFGEGVGNIANFELDQPYLPQGTF 680

Query: 661 KYTIASKDYPEVSYDGTFTVPTSLAYKMASQTI FYPFHAGDTYLRVNPQFAVPKGTDALV 720
KYTIASKDYPEVSYDGTFTVPTSLAYKMASQTI FYPFHAGDTYLRVNPQFAVPKGTDALV
Sbjct: 662 KYTIASKDYPEVSYDGTFTVPTSLAYKMASQTI FYPFHAGDTYLRVNPQFAVPKGTDALV 740

Query: 721 RVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE 779
RVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE
Sbjct: 722 RVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE 800

tr Q6WNQ7 Surface protein BVH-3 [bvh-3] [Streptococcus
Q6WNQ7_STRPN pneumoniae]

1039
AA
align

Score = 475 bits (1222), Expect = e-133

Identities = 239/240 (99%), Positives = 239/240 (99%)

phTE → Query: 1 EVPILEKENQTDKPSILPQFKRNKAQENLKLDEKVVEPKTSEKVEKEKLSETGNSTSNST 60
BVH 3 → Sbjct: 800 EVPILEKENQTDKPSILPQFKRNKAQEN KLDEKVVEPKTSEKVEKEKLSETGNSTSNST 859
Query: 61 LEEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSGEVIKKNMADFTGEAPQG 120
Sbjct: 860 LEEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSGEVIKKNMADFTGEAPQG 919
Query: 121 NGENKPSSENGKVSTGTVENQPTENKPADSLPEAPNEKPVKPENSTDNGMLNPEGNVGSDP 180
Sbjct: 920 NGENKPSSENGKVSTGTVENQPTENKPADSLPEAPNEKPVKPENSTDNGMLNPEGNVGSDP 979
Query: 181 MLDPALIEEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA 240
Sbjct: 980 MLDPALIEEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA 1039

tr Q6WNQ7 Surface protein BVH-3 [bvh-3] [Streptococcus
Q6WNQ7_STRPN pneumoniae]

1039
AA
align

Score = 1059 bits (2738), Expect = 0.0
Identities = 527/528 (99%), Positives = 527/528 (99%)

PH+E
BV#3

Query: 1 MKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDEHKPVGIGHSH 60
MKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDEHKPVGIGHSH
Sbjct: 512 MKDLDDKKIEEKIAGIMKQYGVKRESIVVNKEKNAIIPHGDDHHADPIDEHKPVGIGHSH 571

Query: 61 SNYELFKPEEGVAKKEGKNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPEL 120
SNYELFKPEEGVAKKEGKNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPEL
Sbjct: 572 SNYELFKPEEGVAKKEGKNKVYTGEELTNVVNLLKNSTFNNQNFTLANGQKRVSFSFPPEL 631

Query: 121 EKKLGINMLVVKLITPDGKVLKVS GKVFGEVGNIANFELDQPYLPQGTFKYTIASKDYP 180
EKKLGINMLVVKLITPDGKVLKVS GKVFGEVGNIANFELDQPYLPQGTFKYTIASKDYP
Sbjct: 632 EKKLGINMLVVKLITPDGKVLKVS GKVFGEVGNIANFELDQPYLPQGTFKYTIASKDYP 691

Query: 181 EVSYDGTFTVPTSLAYKMASQTIFYPFHAGDTYLRVNPQFAVPKGTDALVRVFEDEFHGNA 240
EVSYDGTFTVPTSLAYKMASQTIFYPFHAGDTYLRVNPQFAVPKGTDALVRVFEDEFHGNA
Sbjct: 692 EVSYDGTFTVPTSLAYKMASQTIFYPFHAGDTYLRVNPQFAVPKGTDALVRVFEDEFHGNA 751

Query: 241 YLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIIVEVPILEKENQTD 300
YLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIIVEVPILEKENQTD
Sbjct: 752 YLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIIVEVPILEKENQTD 811

Query: 301 KPSILPQFKRNKAQENLKLDEKVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPVTPDPVQE 360
KPSILPQFKRNKAQEN KLDEKVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPVTPDPVQE
Sbjct: 812 KPSILPQFKRNKAQENSKLDEKVEEPKTSEKVEKEKLSETGNSTSNSTLEEVPVTPDPVQE 871

Query: 361 KVAKFAESYGMKLENVLFNMDGTIELYLPSGEVIKKNMADFTGEAPQGNGENKPSSENGKV 420
KVAKFAESYGMKLENVLFNMDGTIELYLPSGEVIKKNMADFTGEAPQGNGENKPSSENGKV
Sbjct: 872 KVAKFAESYGMKLENVLFNMDGTIELYLPSGEVIKKNMADFTGEAPQGNGENKPSSENGKV 931

Query: 421 STGTVENQPTENKPADSLPEAPNEKPVKPENSTDNGMLNPEGNGVSDPMLDPALEEAPAV 480
STGTVENQPTENKPADSLPEAPNEKPVKPENSTDNGMLNPEGNGVSDPMLDPALEEAPAV
Sbjct: 932 STGTVENQPTENKPADSLPEAPNEKPVKPENSTDNGMLNPEGNGVSDPMLDPALEEAPAV 991

Query: 481 DPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA 528
DPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA
Sbjct: 992 DPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA 1039

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UniProtKB/TrEMBL

entry Q9ANY1

[Printer-friendly view](#)[Request update](#)[Q1](#)[\[Entry info\]](#) [\[Name and origin\]](#) [\[References\]](#) [\[Comments\]](#) [\[Cross-references\]](#) [\[Keywords\]](#)
[\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	Q9ANY1_STRPN
Primary accession number	Q9ANY1
Secondary accession number	Q7D4B6
Entered in TrEMBL in	Release 17, June 2001
Sequence was last modified in	Release 17, June 2001
Annotations were last modified in	Release 30, May 2005
Name and origin of the protein	
Protein name	Pneumococcal histidine triad protein E [Precursor]
Synonym	Hypothetical protein SP1004
Gene name	Name: phtE
	OrderedLocusNames: SP1004
From	Streptococcus pneumoniae [TaxID: 1313]
Taxonomy	Bacteria; Firmicutes; Lactobacillales; Streptococcaceae; Streptococcus.

References

[1] NUCLEOTIDE SEQUENCE.

DOI=10.1128/IAI.69.2.949-958.2001; PubMed=11159990 [NCBI, ExPASy, EBI, Israel, Japan]
 Adamou J.E., Heinrichs J.H., Erwin A.L., Walsh W., Gayle T., Dormitzer M., Dagan R., Brewah Y.A., Barren P., Lathigra R., Langermann S., Koenig S., Johnson S.;
 "Identification and characterization of a novel family of pneumococcal proteins (the Pht family) that are protective against sepsis.";
 Infect. Immun. 69:949-958(2001).

[2] NUCLEOTIDE SEQUENCE.

STRAIN=ATCC BAA-334 / TIGR4;
 DOI=10.1126/science.1061217; PubMed=11463916 [NCBI, ExPASy, EBI, Israel, Japan]
 Tettelin H., Nelson K.E., Paulsen I.T., Eisen J.A., Read T.D., Peterson S.N., Heidelberg J.F., DeBoy R.T., Haft D.H., Dodson R.J., Durkin A.S., Gwinn M.L., Kolonay J.F., Nelson W.C., Peterson J.D., Umayam L.A., White O., Salzberg S.L., Lewis M.R., Fraser C.M.;
 "Complete genome sequence of a virulent isolate of Streptococcus pneumoniae.";
 Science 293:498-506(2001).

Comments

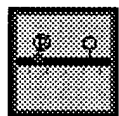
None

Cross-references

AF318956; AAK06761.1; -;
 Genomic_DNA.

[EMBL / GenBank / DDBJ]
 [CoDingSequence]

EMBL AE007403; AAK75121.1; -; [EMBL / GenBank / DDBJ]
 Genomic_DNA. [CoDingSequence]
 PIR H95115; H95115.
 TIGR SP1004; -.
 InterPro IPR006270; Strep_his_triad.
 Graphical view of domain structure.
 Pfam PF04270; Strep_his_triad; 5.
 Pfam graphical view of domain structure.
 TIGRFAMs TIGR01363; strep_his_triad; 3.
 ProDom [Domain structure / List of seq. sharing at least 1 domain]
 HOGENOM [Family / Alignment / Tree]
 ProtoMap Q9ANY1.
 PRESAGE Q9ANY1.
 ModBase Q9ANY1.
 SWISS-2DPAGE Get region on 2D PAGE.
 UniRef View cluster of proteins with at least 50% / 90% identity.

Keywords**Complete proteome; Hypothetical protein; Signal.****Features**

Feature table viewer

Key	From	To	Length	Description
SIGNAL	1	29	29	Potential.

Sequence information

Length: 1039 Molecular weight: 114631 CRC64: 81A563FC806625C4 [This is a checksum on the
 AA Da sequence]

<u>10</u>	<u>20</u>	<u>30</u>	<u>40</u>	<u>50</u>	<u>60</u>
MKFSKKYIAA	GSAVIVLSL	CAYALNQHR	S QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS
<u>70</u>	<u>80</u>	<u>90</u>	<u>100</u>	<u>110</u>	<u>120</u>
QKEGIQAEQI	VIKITDQGYV	TSHGDHYHY	Y NGKVPYDALF	SEELLMKDPN	YQLKDADIVN
<u>130</u>	<u>140</u>	<u>150</u>	<u>160</u>	<u>170</u>	<u>180</u>
EVKGGYIIKV	DGKYVYLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY
<u>190</u>	<u>200</u>	<u>210</u>	<u>220</u>	<u>230</u>	<u>240</u>
TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	Y IPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS
<u>250</u>	<u>260</u>	<u>270</u>	<u>280</u>	<u>290</u>	<u>300</u>
YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	LLKELYDSPA	AQRYSESDGL	VFDPAKIISR
<u>310</u>	<u>320</u>	<u>330</u>	<u>340</u>	<u>350</u>	<u>360</u>
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN
<u>370</u>	<u>380</u>	<u>390</u>	<u>400</u>	<u>410</u>	<u>420</u>
PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA
<u>430</u>	<u>440</u>	<u>450</u>	<u>460</u>	<u>470</u>	<u>480</u>

```

TPSPSLPINP GTSHEKHEED GYGFDANRII AEDESGFVMS HGDHNHYFFK KDLTEEQIKA
      490      500      510      520      530      540
AQKHLEEVKT SHNGLDSLSS HEQDYPSNAK EMKDLDKKIE EKIAGIMKQY GVKRESIVVN
      550      560      570      580      590      600
KEKNAIIYPH GDHHHADPID EHKPVGIGHS HSNYELFKPE EGVAKKEGK VYTGEELTNV
      610      620      630      640      650      660
VNLLKNSTFN NQNFTLANGQ KRVSFSFPPE LEKKLGINML VKLITPDGKV LEKVSQKVFQ
      670      680      690      700      710      720
EGVGNIANFE LDQPYLPGQT FKYTIASKDY PEVSYDGTFT VPTSLAYKMA SQTIFYPFHA
      730      740      750      760      770      780
GDTYLRVNPQ FAVPKGTDAL VRFDEFHGN AYLENNYKVG EIKLPIPKLN QGTTRTAGNK
      790      800      810      820      830      840
IPVTFMANAY LDNQSTYIVE VPILEKENQT DKPSILPQFK RNKAQENLKL DEKVEEPKTS
      850      860      870      880      890      900
EKVEKEKLSE TGNSTSNSTL EEVPTVDPVQ EKVAKFAESY GMKLENVLFN MDGTIELYLP
      910      920      930      940      950      960
SGEVIKKNMA DFTGEAPQGN GENKPSENGK VSTGTVENQP TENKPADSLP EAPNEKPVKP
      970      980      990     1000     1010     1020
ENSTDNGMLN PEGNVGSDPM LDPALEEAPA VDPVQEKLEK FTASYGLGLD SVIFNMDGTI
      1030
ELRLPSGEVI KKNLSDLIA

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Q9ANY1 in FASTA
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BLAST submission on
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Sequence analysis tools: ProtParam, ProtScale,
Compute pI/Mw, PeptideMass, PeptideCutter,
Dotlet (Java)



ScanProsite, MotifScan



Submit a homology modeling request to SWISS-
MODEL



NPSA Sequence analysis
tools



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